VOLUME XXVI NUMBER 1

DISEASES

of the

CHEST

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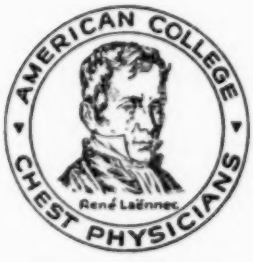

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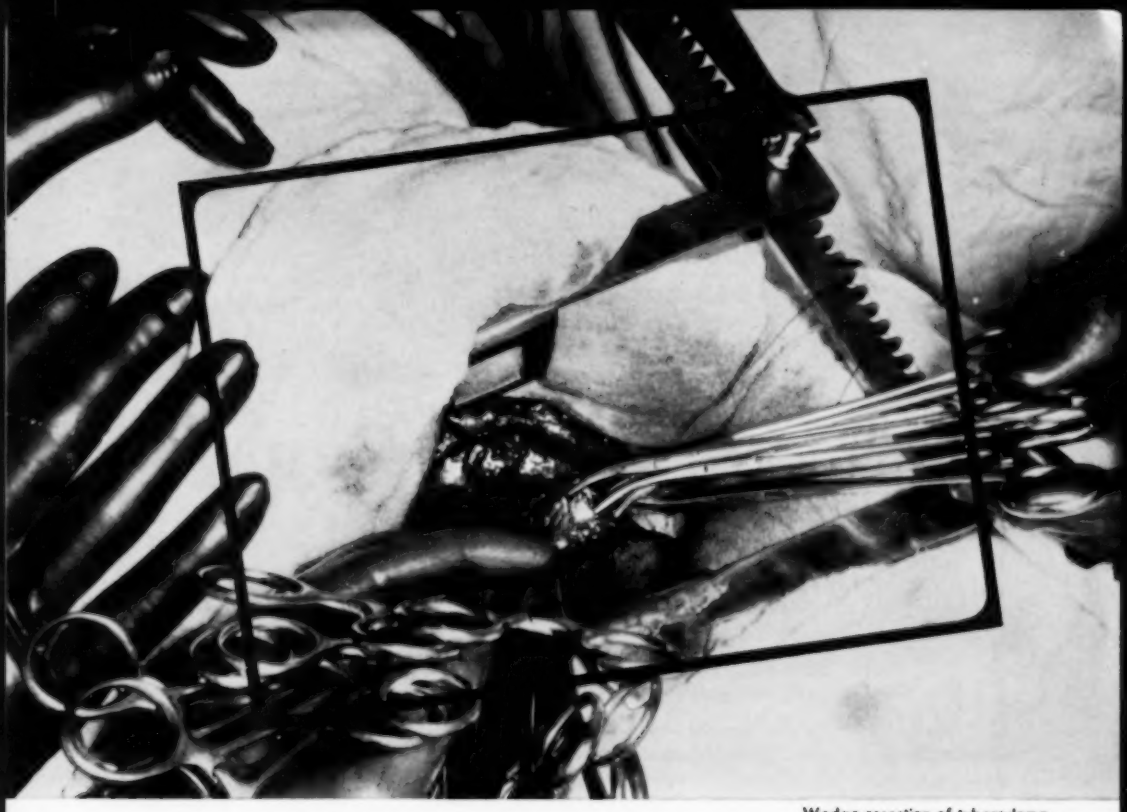

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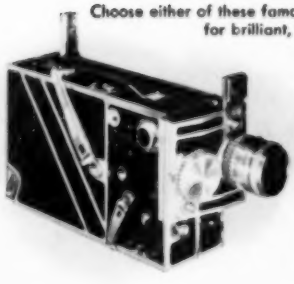

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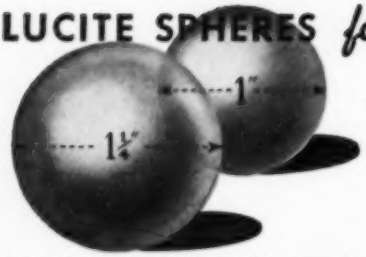

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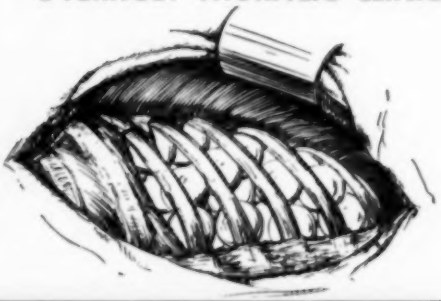

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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tuberc. 67:808, 1953.

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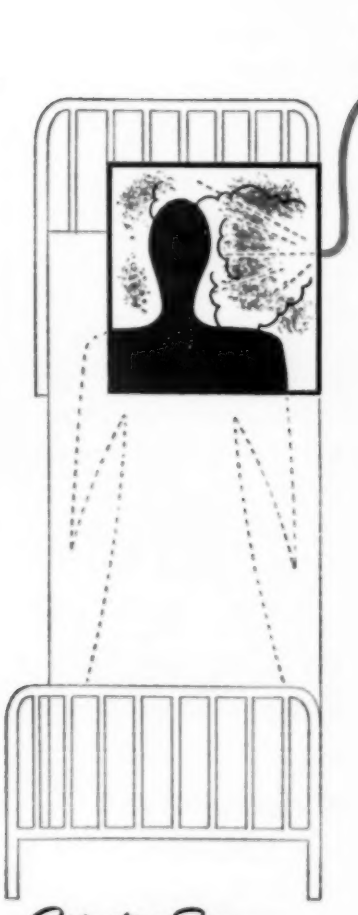

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1. Sadove, M.S.: Paper read at Meeting of the Champaign County Medical Society, Champaign, Ill., Mar. 12, 1953.

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**Heck, W.E.; Lynch, W.J., and Graves, H.L.: Acta oto-laryng. 41:416, 1953.*

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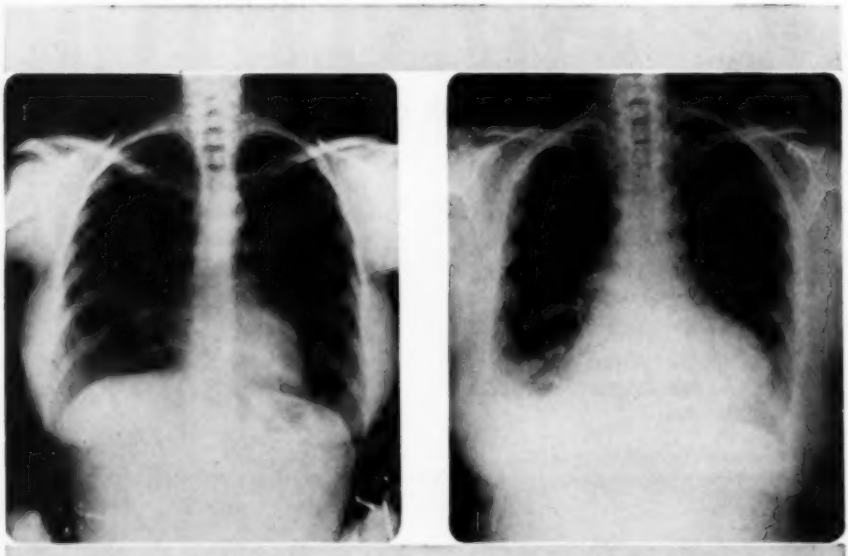

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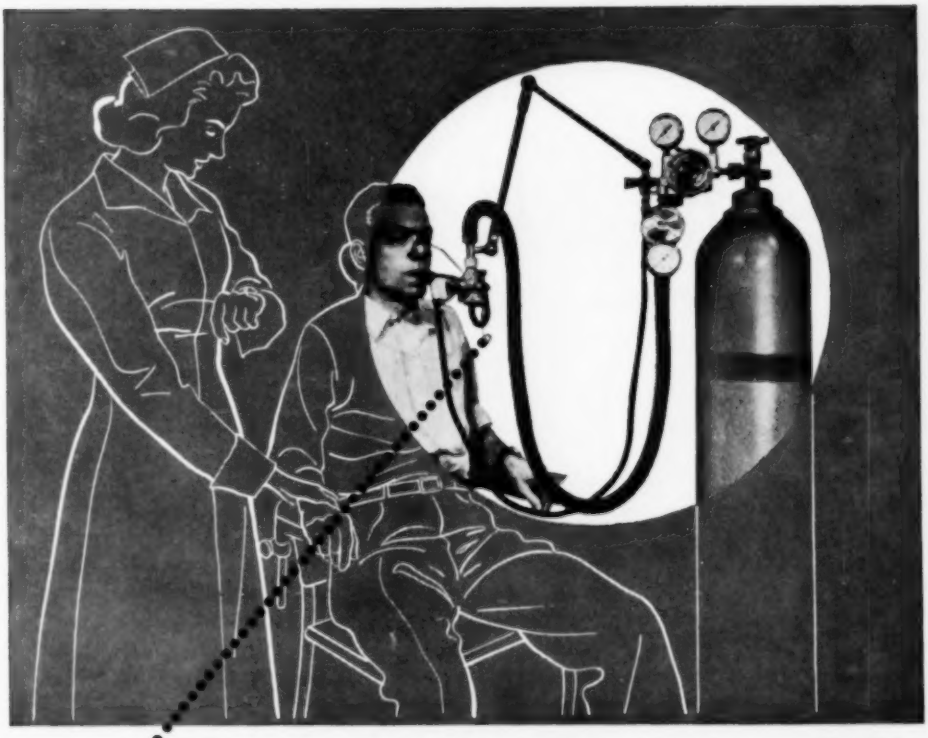

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Modern Chemotherapy of Infectious Diseases; Implications and Significance*

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Disease and life appear to be indivisible and what is designated as health is in fact a state of relativity. Foremost as the cause of man's multitudinous ailments are infectious agents which are said to account for 40 to 50 per cent of all diseases to which human beings are subject.[1] This is not surprising when it is realized that there exist approximately 250 living agents of vegetable and animal origin that have been recognized as capable of producing infection in man.[1] Furthermore, the ubiquitous distribution of microorganisms of potential pathogenicity in homologous and heterologous hosts, in soil, water and atmospheric air provides ample opportunity for exposure. Fortunately, except in epidemics, exposure results in demonstrable disease in a relatively small percentage of the population at any one time. Man's intrinsic resistance, developed through the ages, usually provides an unfavorable threshold capable of suppressing a large percentage of microorganisms which if conditions be propitious may be capable of serious consequences.

Nevertheless, diseases due to microorganisms have been and are likely to continue to be a major problem in medicine and the cause of concern and of considerable illness in man throughout the world. Some have believed that it is within the scope of man's ingenuity to free himself from all microbial parasites and thus be emancipated from the curse of infections. This is a commendable and optimistic outlook which might appropriately be assigned to the realm of fantasy. Although improved sanitation, better nutrition and the so-called wonder drugs have contributed significantly to the conflict of man against infections, final victory is not likely in the foreseeable future.

The general acceptance during the past decade of chemotherapeutic agents as a means of treating a long list of infectious diseases is probably the most significant development in modern medicine. This acceptance

*Read as moderator's address at session on infectious diseases of symposium on The Modification of Structural Changes in Infectious, Neoplastic, and Other Diseases Following Use of Modern Chemotherapy, at the meeting of the American Association of Pathologists and Bacteriologists, St. Louis, Missouri, April 2-4, 1953.

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of a new approach to therapeutic problems that were often difficult and frequently intractable is related to (1) general effectiveness; (2) convenience; (3) frequent discovery of new substances, particularly antibiotics; (4) promotional activities by those who produce and sell such products and (5) the naive confidence of the nonmedical public and the noncritical acceptance by many physicians of the enthusiastic accounts of the performance of new so-called miracle drugs which appear frequently in medical and nonmedical publications. As a nation we are indeed well read, if not too well informed, in those realms of medicine in which the public has a marked curiosity often based on fear.

We are well into an era of promiscuous therapeutics in which the per capita consumption of the newer chemotherapeutic substances is probably second only to that of aspirin. These substances have a varied and complex chemical composition. They are being used extensively, often without valid justification and in many instances for prolonged periods in treating chronic infections such as tuberculosis. Although these newer medicaments are prescribed with therapeutic intent, they are, like most drugs, potentially poisonous. These agents have the capacity to combat successfully many infections that previously presented formidable therapeutic obstacles; yet they may under appropriate but often obscure circumstances be capable of harmful effects of varying degrees of severity.

It is, therefore, timely that physicians and pathologists examine the situation and determine what structural modifications, beneficial and otherwise, have resulted as a consequence of what has become truly an amazing development of a phase of materia medica that is still in its infancy.

Since the discovery by Domagk (1935)[2] of the antibacterial action of prontosil the treatment of infectious diseases by specific agents has progressed to an extraordinary degree. Millions of people are the recipients annually of chemotherapeutic substances prepared synthetically or obtained by microbial growth. These agents are prescribed not only therapeutically but also prophylactically. Administration may be limited to one course or more frequently the drugs are taken on several to numerous occasions during a period of years. The drugs may be given singly or in combination with one or several agents having the same or markedly different bacterial spectra depending upon the ingenuity and perhaps the caprice of the physician. These remarks are not intended to depreciate the real worth of the newer chemotherapeutic agents in the treatment of many infectious diseases. Their value is substantial and, in some situations, their use may mean the difference between life and death.

Production Volume of Medicinal Agents

The ever-increasing use of medicinal chemicals has created a demand, the volume of which seems incredible. According to figures derived from a report of the United States Tariff Commission the production of synthetic chemicals for medicinal use reached an all-time high in 1951.[3] The total output for that year is given as 73,543,000 pounds which represents an increase of 49 per cent over 1950. To emphasize the magnitude of the

1951 production of medicinals and its practical implications one need only point out that the amount represents nearly one-half pound for every man, woman and child in the United States. Production figures for a few of the more commonly used drugs are of some interest: aspirin, 13,481,000 pounds; salicylic acid, 7,842,000 pounds; vitamins, 2,546,000 pounds; barbituric acid derivatives, 789,000 pounds; the so-called sulfa drugs, 6,411,000 pounds and antibiotics, 1,286,000 pounds. To mention but two of the antibiotics, it has been estimated that the world production of crystalline penicillin is approximately 300,000 kg. annually. This amount is considered sufficient to treat more than 4,000,000 patients per month.[4] Chloramphenicol, during the five years from the time of discovery in 1947, was prescribed for more than 8,000,000 people.[5]

The medicinal agents which are produced in the United States by more than 1,100 establishments that manufacture drugs, biological products and pharmaceutical preparations finally reach the ultimate consumer through the medium of approximately 50,000 drug stores.[6] While such drugs as aspirin and the vitamins are available without prescription it appears that approximately 150,000 practicing physicians issue a total of more than 300,000,000 prescriptions annually.[6]

The preceding brief account of the volume of production of medicinals is not given in a sense of disparagement. It can be properly said that the drug and pharmaceutical industry has contributed most significantly to modern medicine by providing a long list of new drugs of genuine therapeutic value often, during the developmental stage, at considerable financial risk. That the industry has been alert and imaginative is suggested by the statement that more than half of the drugs prescribed in 1951 were unknown in 1940.[6] This development has an interesting and important connotation for the future. New medicinals require a continuing if not an increased awareness of potential hazards. The vigilance of physicians and pathologists is likely to be a widening rather than a narrowing responsibility if patients who receive new drugs in the future are to do so with reasonable assurance of their relative safety. In all probability there will always be some risk. In instances of serious and intractable infections the risk must be balanced against possible consequences to the patient if specific chemotherapy is withheld. The preceding remarks constitute a somewhat sketchy account of the present trends in the production of medicinal substances designed to prevent or alleviate if not to cure human illnesses. The ability of scientists to discover new drugs and the skill of modern chemical engineers to produce the products appear to be exceeded only by the capacity of the human organism to consume that which is offered.

Modern Chemotherapeutic Agents

If one dates the present era of extensive clinical chemotherapeutic practice from 1935 when Domagk[2] reported that the development of otherwise fatal hemolytic streptococcal infections in mice could be prevented with prontosil there has been developed a considerable number of useful chemotherapeutic agents which can be grouped conveniently into two categories.

TABLE I
CURRENTLY IMPORTANT SULFONAMIDES AND OTHER SYNTHETIC ANTIMICROBIAL AGENTS

DRUG	ADMINISTERED	INDICATIONS FOR CLINICAL USE	POSSIBLE TOXIC EFFECT
4,4'-diaminodiphenyl-sulfone	Orally	Leprosy	Neuritis, dermatitis, hemolytic anemia, acute yellow atrophy, psychosis
Promin	Orally or intravenously	Leprosy	Hemolytic anemia and leukopenia
Sulfapyridine	Orally	Pneumonia, meningitis, genitourinary infections	Hematuria, obstructive renal crystallization, hepatitis, hemolytic anemia
Sulfacetimide	Orally	Urinary tract infections due to Escherichia coli	Minor consequences
Sulfathiazole	Orally	Pneumonia, staphylococcal septicemia, osteomyelitis	Skin rash, hematologic disturbances
Sulphetrone	Orally	Leprosy	Transient anemia
Sulfadiazine	Orally	Pneumonia, meningitis, urinary tract infections	Skin rash, hepatitis, hematologic disturbances
Sulfamerazine	Orally	Pneumonia, meningitis, sepsis due to gram-positive bacteria	Skin rash, fever, hepatitis, hematologic disturbances
Sulfaguanidine	Orally	Bacillary dysentery, prophylactically before colonic surgery	Skin rash and fever
Sulfamethazine	Orally	Urinary tract infections, pneumonia, meningitis	Similar to sulfadiazine
Gantrisin	Orally	Urinary tract infections, pneumonia, streptococcal and staphylococcal infections	Urticaria, hematuria, hematologic disturbances
Para-aminosalicylic acid (PAS)	Orally	Tuberculostatic adjuvant	Gastrointestinal irritation, diarrhea, drug fever, dermatitis
Isonicotinic acid hydrazide (isoniazid)	Orally	Tuberculosis	Vertigo, convulsions, psychosis, dermatitis, hepatitis with jaundice, hemopoietic disturbances, drug fever, peripheral neuritis

One group consists of the important and most commonly used synthetic organic compounds including the sulfonamides. The second group consists of the most useful and widely used antibiotics (Tables I and II).

There has been a tendency during the past few years to refer to all substances that are antagonistic to microbial infections as antibiotics. The accepted definition of this word does not justify such usage. The term has a more precise meaning. An antibiotic may be defined as a chemical compound which is produced by and obtained from certain living cells, especially cells of lower plant life such as bacteria, yeasts and molds, and which is antagonistic to other forms of life such as pathogenic bacteria or other microorganisms.[7]

The term "chemotherapy" is more inclusive, meaning the use of drugs in the treatment of systemic infections. If one accepts the definition of chemotherapy literally, compounds of antibiotic character also are chemotherapeutic agents. However, some insist and for valid reasons that a chemotherapeutic agent denotes a well-defined chemical substance, usually prepared synthetically, and is thus distinguished from an antibiotic agent, which is obtained by extracting and purifying substances of microbial growth, the chemical constitution of which has not been established precisely.[8] For reasons of definitive expression the treatment of infections by drugs might therefore be designated antibiotic therapy or chemotherapy depending upon the nature of the medicinal substance. For practical purposes where definitive expression is not essential the use of the term "chemotherapy" as indicating the prevention and treatment of infections with drugs has many advantages. One should not, however, refer to all chemotherapeutic agents as antibiotics.

Misuse and Hazards of Chemotherapy

The hazards of antimicrobial therapy depend upon several factors. These include (1) the nature of the chemotherapeutic agent; (2) whether it has been used previously in the same patient; (3) impairment of excretory function; (4) the size of the dose and duration of therapy and (5) the emergence of resistant or drug-fast bacterial populations as a consequence of the widespread and perhaps excessive use of antimicrobial drugs. Fortunately the administration of the presently useful chemotherapeutic substances is, in most instances, not followed by recognized signs of intolerance. However, it is important to recognize that under certain, and sometimes subtle, physiologic situations, untoward effects often of a serious nature do occur.

Toxic effects of the chemotherapeutic agents most widely used at the present time involve many of the important organs of the body. The sites of predilection include the skin, the central and the peripheral nervous systems, the mucosa from the mouth to the anus, the liver, the kidneys, certain elements of the hormonal system and the hemopoietic tissues. The toxic impact indicative of drug intolerance may vary in intensity from a mild indisposition of no consequence to grave illness that may be violent or even catastrophic in nature. Examples of the more serious effects of

TABLE II

CURRENTLY IMPORTANT MEDICINAL ANTIBIOTICS

ANTIBIOTIC	ADMINISTRATION	INDICATIONS FOR CLINICAL USE	POSSIBLE TOXIC EFFECTS
Penicillin	Parenterally and orally	Infections due to gram-positive bacteria	Neurologic irritation, glossitis, stomatitis, allergic reactions, urticaria and "therapeutic shock"*
Streptomycin and dihydro-streptomycin	Parenterally	Tuberculosis, plague and combination therapy with other drugs	Neurotoxicity, drug fever, dermatitis
Bacitracin	Topically	Infections due to gram-positive bacteria	Nephrotoxicity
Polymixin	Intramuscularly	Infections due to Pseudomonas and Hemophilus influenzae	Neurotoxicity and nephrotoxicity
Chloramphenicol	Orally	Typhoid and rickettsial infections	Stomatitis and suppression of hemopoiesis
Aureomycin	Orally	Against gram-positive and gram-negative pathogens and rickettsial diseases	Gastrointestinal irritation, glossitis, pruritus and cutaneous allergy
Neomycin	Intramuscularly	Infections of the urinary tract due to gram-negative organisms	Nephrotoxicity, deafness
Terramycin	Orally	Bacteremia or peritonitis due to Bacteroides infections. Rickettsial infections	Nausea, vomiting, diarrhea, stomatitis, skin rash
Viomycin	Orally	Infections due to streptomycin-resistant tubercle bacilli	Neurotoxicity, blood electrolyte disturbances
Erythromycin	Orally	Infections due to gram-positive bacteria including penicillin-resistant staphylococci	Insufficient data

*So-called Jarisch-Herxheimer reaction in syphilis.

drug toxicity include exfoliative dermatitis, aplastic anemia, hepatitis and psychosis. Especially serious are disturbances of the gastrointestinal tract that may occur following the oral administration of the broad spectrum antibiotics. In these instances suppression of the normal intestinal flora may permit the ascendancy of Micrococcus pyogenes resistant to one or several antimicrobial substances. The resultant superinfection has serious connotations. Death has resulted in several instances.[9,10]

The development of our present chemotherapeutic armamentarium evolved largely from the selection of substances effective particularly in acute infections such as those due to streptococci and pneumococci. However, a few of the agents have proved useful medicinals in the treatment of infections of varying degrees of chronicity. In most instances the duration of therapy and the volume of drug administered are related to the chronicity of the infection. Administration of drugs extending for periods of several weeks to several months or to a year or longer is not unusual. In these instances, drugs that are ordinarily well tolerated when used in acute infections when only a relatively few doses are necessary may when used for prolonged or indefinite periods have an accumulative toxic effect. Such effects may escape detection until irreversible harm has been done.

To use chemotherapeutic agents indiscriminately or promiscuously is not only empiricism but a serious dereliction of professional responsibility. During the past decade extensive experience by competent investigators and clinicians has yielded much important information concerning the practices of chemotherapy. As a consequence guideposts are available whereby the physician can prescribe these modern therapeutic agents with reasonable assurance that no serious toxic consequences will ensue.[9,11,12] Clinical use of chemotherapy should be restricted for specific medications in doses that can be safely tolerated and for periods of time no greater than are required to suppress or eliminate the offending microorganisms. In other words the use of these drugs should be based on a definite diagnosis indicating their need. They definitely "should not be employed as therapeutic panaceas for minor nondescript ailments."[13] Otherwise, as Finland and Weinstein[9] have said, "A simple or mild disease may be converted to one that is serious and potentially fatal."

Factors Influencing Results of Chemotherapy

The practice of chemotherapy involves more than the antiseptic action of a drug. The use of a new drug clinically should be predicated upon experimental trials in animals and not upon antimicrobial action *in vitro* regardless of how impressive the latter may be. Only by bringing the antibacterial substance in contact with the infected tissue within the body of the host can one determine the potentialities of a drug to modify an infective process. Involved importantly in *in vivo* procedures is the innate defense mechanism of the host as it responds to the infection in an attempt to circumvent the pathogenicity of the microbial invaders. Furthermore, in *in vivo* procedures the drug is exposed to physiological, biological and anatomical factors which alter its antimicrobial action.

These factors may inactivate partially or completely substances having a highly effective potential *in vitro*.

Those concerned with the administration of new antimicrobial agents to patients should be reminded of the pitfalls inherent in attempting to transfer results obtained in one species to another species. Conclusions as to the therapeutic efficacy of a specific drug based on experiments on animals should be viewed with circumspection when the drug in question is considered for use in man.[14]

Pharmacological data obtained on new drugs by tests on animals are of the utmost value; however, such data may prove to be misleading or inadequate when the drug is administered to patients. Pharmacological tests are usually performed on normal intact animals whereas in clinical practice the drug is placed in a markedly different biological economy. The patient represents a species different from that used in the experimental trials and has suffered a derangement of normal physiology as a consequence of an infection. Infection in the patient may be mild or severe, acute or chronic, localized or disseminated, and may be associated with varying degrees of malnutrition, metabolic disturbances, vascular alterations, dehydration and structural changes. These complex physiochemical factors may be of much significance in determining the final results of a therapeutic regimen.

Basically, however, the effectiveness of chemotherapy, its success or failure, is largely dependent upon (1) the sensitivity of the infectious agent to the antimicrobial substance; (2) the potential availability of natural or acquired cellular factors of defense that become activated in response to the infectious agents; (3) the nature of the lesion and its anatomic situation[15,16] and (4) the tolerance of the individual patient for the drug.

An effective chemotherapeutic agent will for a time exert a deterrent effect upon the growth and multiplication of microbial cells and may in fact be lethal to some of the infective parasites. However, the final triumph of the host over pathogenicity is dependent upon sustained mobilization of innate host defenses which have been able to operate more effectively as a consequence of the medicinal ally. When the natural defense factors of the host are deficient, as for example in infancy or old age, or are depressed or debilitated as a consequence of severe stress, antimicrobial agents, ordinarily highly effective, are likely to prove inadequate. Successful chemotherapy requires the co-ordinate action of an effective antimicrobial substance of high specificity and of low toxicity and a responsive defense economy operating at an effective level. Without the latter, chemotherapy is at best a palliative measure destined to fall far short of expectations.

We may now examine briefly the basic objective of chemotherapy and what can be accomplished by the successful use of these newer therapeutic weapons. First, I would emphasize that chemotherapeutic substances are drugs directed against the cause of the disease and not against the symptoms. The purpose of chemotherapy is essentially to prevent, abort or interfere with the pathogenesis of the infective process. The specific mech-

anism which enables a therapeutic agent to suppress, kill or render impotent the infective parasites is, for most drugs, not clearly established.

Resolution of the cellular increment laid down as a consequence of the host's reaction to the infection is not the task of the chemotherapeutic agent per se. The successful interference with the host-parasite relationship of microbial pathogens by chemicals or by components of the intrinsic defense mechanism may have a marked influence upon factors that initiate and sustain the process of healing and repair. As a consequence of lessening the pathogenic impact, tissue reactions may be modified. Necrobiosis and other retrogressive phenomena may be reduced to a minimum and the dynamics of repair may proceed in some instances at an accelerated tempo.

In chronic infections in which structural changes have occurred before chemotherapy is instituted the basic function of the therapeutic substance is to create or contribute to an unfavorable microbial economy. If the drug is sufficiently effective in its antimicrobial action the lesions cease to progress. However, resolution or regression of the lesions does not necessarily follow regardless of how complete the antagonistic action of the chemotherapeutic substance may be against the microorganisms responsible for the lesions. Depending upon their size, structural character, extent of necrosis, duration and anatomic situation, the lesions associated with chronic infections usually persist as residual reminders of the disease long after the etiologic agent has ben rendered inert, is dead or has disintegrated.

In examining tissues for modifications of the structural changes as a consequence of chemotherapy the pathologist should search for and recognize structural signs of possible toxicity of the medicinal agent. This is especially important when new chemotherapeutic substances are first submitted to clinical trials and in those situations in which the type of infection requires specific therapy of long duration. Tissues that should be examined for structural signs of toxic effects include the central nervous system, the gastrointestinal tract, the kidneys, liver, bone marrow and components of the endocrine system.

Final Comment

As new chemotherapeutic agents are found and applied in clinical medicine there must be maintained a constant awareness for untoward effects. So far, there has not been discovered any effective chemotherapeutic substance that is devoid of potential toxicity. Perhaps no drug administered orally or parenterally is entirely without some hazard. A small but definite risk should be recognized and a compromise attained between the good that may be accomplished and the possibility, even remote, that undesirable effects of variable degrees of seriousness may ensue.

The safety of chemotherapeutic procedures is best assured when the responsibility is shared by those who by training and experience are aware of the hazards, and are capable of recognizing untoward reactions early in their inception. Those directly concerned include the internist, the clinical pathologist, the hematologist, the medical bacteriologist, the

dermatologist, the pathologist, the neurologist, and occasionally the psychiatrist.

By virtue of the course of events it is the pathologic anatomist who must in most instances detect and interpret the structural changes that may have occurred as a direct or indirect consequence of chemotherapy. This does not imply that fatalities as a direct result of chemotherapy are of common occurrence. Such is not the case. However, many deaths have been recorded in which there seemed to be a significant relationship between the therapeutic regimen and the fatal termination. Even though death may not be related to recent exposure to chemotherapy, the pathologist should be alert to the presence of signs of latent effects of drug therapy given weeks, months or years previously. If the present trend in the widespread use of chemotherapy continues with a large percentage of the population receiving antimicrobial agents intermittently throughout life, structural changes at present unpredictable may eventually be found frequently. Certainly this possibility will deserve careful attention.

Pathologists are well aware of the many structural changes of subtle character that are difficult to recognize or interpret definitively. This is especially true in certain infectious diseases in which it is difficult to recognize or to understan all the varied, complex and obscure factors that finally result in the formation of a lesion. The picture may become additionally difficult to interpret because of the influence on the defense factors of the body of the variable and complicated chemical components of the multiplicity of chemotherapeutic agents which may have been administered.

Although the lesion or focus of the infection may concern primarily or be limited to a single organ, in chemotherapy, unless the drug is administered topically, it is necessary to expose the entire body economy—normal as well as morbid tissues—in order to reach the target. In some situations this widespread or systemic distribution of an antimicrobial agent has certain advantages, as when new or undisclosed foci of infection, removed from the primary foci, are exposed to the therapeutic agents. Bacteremias are likewise combated more effectively when the drug enters the blood stream.

Despite the desirable attributes of systemic medication there are certain objectionable features. In some situations systemic medication is not necessary and may be objectionable. If it were possible by some practicable means to isolate the area that is to receive the medicinal agent or if there existed a mechanism whereby chemotherapeutic substances would by selective chemical attraction reach the morbid area only, the question of toxicity in chemotherapy might be reduced to a minimum.

In closing this brief essay much that is of theoretical as well as factual interest in the realm of chemotherapy has been omitted. This phase of medicine, which Ehrlich[17] launched so auspiciously nearly 50 years ago but which was the cause of continued disappointment until the advent of prontosil, now constitutes a major industry and is of paramount importance to physicians. Furthermore, modern chemotherapy has made an inestimable

contribution to human welfare. The recipients of military and of civilian medicine have benefited tremendously from the apparently never-ending list of new antimicrobial agents. For physicians to keep fully informed regarding the precise therapeutic indications and possible untoward side effects of all new medicinal substances would indeed be an arduous if not an impossible task. Fortunately, agents developed by reputable pharmaceutical concerns and approved by the Council on Pharmacy and Chemistry and by the Federal Food and Drug Administration can usually be accepted with confidence.

As more information is obtained by scientific inquiry and by accurate observation, the newer antimicrobials will be used with more discrimination and effectiveness. Many of these substances have become indispensable medicinals and represent a remarkable revolution in the clinical management of infectious diseases. Modern medicine is, I believe, thoroughly capable of coping successfully with the varied and complex difficulties which may be associated with this form of therapeutics. As the problems become more clearly defined and the implications more fully realized, the safety and effectiveness of modern chemotherapy will be enhanced.

In conclusion, I should say that the purpose of my preceding remarks is not to invite distrust of a very substantial development in the treatment of infectious diseases. Rather my intentions have been to provide a basis for a better understanding of factors involved in modern chemotherapy in order that these useful drugs may be used with greater safety and that their maximal antimicrobial potentials may be realized in the care of the sick.

SUMMARY

The trends in modern chemotherapeutic practice have been examined, and the implications and significance of the widespread and frequently indiscriminate use of medicinals, all of which have potential toxicity, have been emphasized. The annual production of chemical agents in the United States for therapeutic use has attained a volume that is almost incredible, and it is estimated that 150,000 physicians issue a total of more than 300,000,000 prescriptions annually.

The substantial value of modern chemotherapeutic agents is recognized. When used with circumspection, many synthetic and antibiotic agents have life-saving potentialities. However, many of these medicinals, if prescribed unwisely, are definitely hazardous. This is particularly true of agents having a broad antibacterial spectrum and in situations where chemotherapy is continued for prolonged periods of time.

The points stressed in this paper include:

1) The vigilance of internists and of pathologists must be a continuing responsibility if patients who receive new drugs in the future are to do so with reasonable assurance of their safety. It is pointed out that the sites of predilection for toxic effects include some of the most vital organs of the body, and that the toxic impact in some instances may be violent or even catastrophic in nature.

2) Chemotherapeutic agents should be directed primarily against the cause of the disease and not against the symptoms.

3) Assuming that the infective agent is sensitive to the antibacterial substances prescribed, successful chemotherapy depends upon the united action of an effective antimicrobial agent of high specificity and of low toxicity, with the intrinsic defense mechanisms of the body operating at an effective level. Resolution of the cellular constitutents occurring as a consequence of the host's reaction to the infection is not the task of the chemotherapeutic agent per se.

4) The possibility of latent effects of drug therapy received months or years previously must be recognized. If the widespread use of chemotherapy continues, with a considerable percentage of the population receiving antimicrobial agents intermittently throughout life, structural changes of grave significance at present unpredictable may eventually ensue.

5) Chemotherapeutic agents should not be prescribed indiscriminately or promiscuously. Their use should be restricted for specific medications in doses below the toxic level and for periods of time no greater than necessary to suppress or render impotent the infective microorganisms.

RESUMEN

Se han examinado las tendencias en la práctica quimioterápica moderna y las consecuencias y significación del frecuente uso con gran amplitud y sin juicio de los medicamentos que tienen, según se recalca, una potencial toxicidad. La producción anual de agentes químicos en los Estados Unidos ha alcanzado cantidades increíbles y se estima que los 150,000 médicos en el País, producen 300,000,000 de prescripciones al año.

Se reconoce el valor substancial que los agentes terapéuticos modernos tienen. Cuando se usan con prudencia, muchos agentes antibióticos y sintéticos tienen potencialidades capaces de salvar la vida. Sin embargo, muchos de estos medicamentos si se prescriben imprudentemente son definidamente peligrosos. Esto es especialmente cierto tratándose de los medicamentos que tienen un amplio campo de acción bacteriana y cuando la quimioterapia es prolongada.

Los puntos recalcados en este trabajo son:

1) Debe quedar bajo la responsabilidad del internista y del patólogo el enfermo que recibe drogas nuevas, si se espera que éste esté relativamente seguro. Se señala que los lugares de predilección para los efectos tóxicos, corresponden a algunos de los órganos más vitales de modo que el impacto en algunos casos puede ser violento y catastrófico.

2) Los agentes terapéuticos deben dirigirse en primer lugar, contra las causas de la enfermedad y no contra los síntomas.

3) Suponiendo que el agente infectante es sensible a las substancias antibacterianas prescritas, su éxito depende de dos cualidades unidas: efecto antibacteriano altamente específico y de baja toxicidad de manera que los mecanismos defensivos del organismo se conserven sin deprimirse. La resolución de la afección celular, depende de la reacción del huésped y no es consecuencia de la tarea del agente quimioterápico por sí mismo.

4) Hay la posibilidad de efectos latentes de una droga recibida meses o años antes. Si el amplio uso de los quimioterápicos continúa, con un considerable porcentaje de la población recibiendo agentes antimicrobianos intermitentemente a través de su vida podría haber cambios estructurales que actualmente no pueden preverse.

5) Los agentes quimioterápicos no deben prescribirse indiscriminadamente o promiscuamente. Su uso debe restringuirse a la medicación específica en dosis debajo del nivel tóxico y por tiempo no mayor del necesario para volver impotente el micro-organismo infectante.

RESUME

L'auteur fait l'examen des tendances modernes de la chimiothérapie. Il insiste sur les conditions de l'utilisation généralisée et souvent sans discrimination de produits qui ont tous un potentiel toxique. La production annuelle de produits chimiques à usage thérapeutique à atteint aux Etats-Unis une proportion véritablement incroyable. On estime que 150,000 médecins font chaque année plus de 300 millions d'ordonnances concernant ces produits.

On reconnait l'incontestable valeur des agents chimiothérapiques modernes utilisés avec circonspection, beaucoup de produits synthétiques et d'antibiotiques peuvent sauver la vie. Toutefois, beaucoup de ces drogues sont dangereuses si elles sont prescrites sans discernement. Ceci est particulièrement vrai quand il s'agit de produits dont le spectre antibactérien est large, et dans les cas où l'on prolonge leur administration pendant une longue période. Les points sur lesquels insiste l'auteur sont les suivants:

1) La responsabilité des médecins doit être continuellement en éveil si l'on veut que les malades à qui l'on prescride nouveaux produits soient traités avec l'assurance certaine que cela ne nuira pas à leur sécurité. L'auteur met l'accent sur le fait que les effets toxiques se portent avec prédilection sur les organes les plus importants du corps, et que l'action toxique dans certains cas peut être violente et même catastrophique.

2) Il faut que les agents chimiothérapiques soient avant tout utilisés contre les causes de la maladie et non contre ses symptômes.

3) Etant entendu que l'agent infectieux est sensible à la substance antibactérienne prescrite, pour que la chimiothérapie soit efficace, il feut que s'unissent l'action effective d'un agent antimicrobien de haute spécificité et de basse toxicité et les moyens propres de défense de l'organisme. L'action cellulaire qui survient à la suite de la réaction de l'organisme atteint par l'infection ne peut être effectuée par l'agent chimiothérapique à lui seul.

4) Il faut reconnaitre la possibilité des effets latents qui doivent être attribués à un traitement médicamenteux reçu des mois ou des années auparavant. Si le chimiothérapie continue à être répanduce comme elle l'est, avec un nombre considérable d'individus recevant de temps en temps un traitement antimicrobien au cours de leur vie, il est possible que surviennent de graves altérations de structure qui sont pour le moment imprévisibles.

5) Les agents chimiothérapiques ne devraient pas être prescrits sans discrimination et de façon anarchique. Leur utilisation devrait être limitée à des traitement spécifiques, à doses inférieures au niveau toxique, et pour des période de temps qui ne doivent pas excéder celles qui sont nécessaires pour supprimer ou rendre inactifs les micro-organismes infectants.

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The Virulence of Isoniazid Resistant Tubercle Bacilli, Recovered from Patients During Treatment

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Tubercle bacilli, resistant to isoniazid, isolated from sputum of patients during treatment with isoniazid, show varying loss of their virulence for guinea pigs. Virulence is judged by the ability to produce macroscopic tuberculosis with positive cultures and by the rapidity to spread (generalise) in the guinea pig.

Materials and Methods.

For infection of animals control-cultures from the sensitivity tests were used. These were always the first subcultures on solid egg medium about four weeks old. The cultures were resistant to isoniazid, but susceptible to streptomycin, para-aminosalicylic acid and conteben. They were weighed wet, suspended in normal saline and injected subcutaneously in the right inguinal region. The guinea pigs were killed after different periods.

If the degree of severity of tuberculosis for each organ is designated with the numbers 0.5-4, it is possible, to lay down an *index of the macroscopic tuberculosis* for each guinea pig, which represents the sum of the numbers obtained from the different organs: inguinal nodes right and left, iliac nodes, spleen, liver, lungs and paratracheal nodes. *(Fust a. Studer, Meissner, Steenken a. Wolinsky.)*

If the same seven organs are cultivated separately, it is possible, to lay down a *cultural index for tuberculosis* for each guinea pig, which represents the sum of the positive organs. *(Meissner.)*

The isoniazid susceptibility of each culture (the primary cultures from the sputum as well as each culture from the different organs from guinea pigs) was tested on solid egg medium (modified Hohn IV, diluted with liquid Sauton medium) as indicated by the "Deutsches Zentralkomitee zur Bekaempfung der Tuberkulose". From the primary egg medium culture about 0.5 mg. (wet weight) per ml. were suspended in normal saline (turdibity comparison), one loopful (3 mm.) from this dilution was inóculated on each medium. The tubes were plugged with cotton wool, which was dipped in molted paraffin. Readings were taken after three weeks incubation at 37 degrees C.

The different degrees of susceptibility were defined as follows:

Susceptible=no growth on solid medium, containing 0.1 mcgm. isoniazid per ml.

Nearly susceptible=growth on medium, containing 0.1 mcgm., no growth on medium, containing 1.0 mcgm. isoniazid per ml.

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Moderately susceptible=growth on medium, containing 1.0 mcgm., no growth on medium, containing 10 mcgm. isoniazid per ml.

Resistant=growth on medium, containing 10 mcgm. isoniazid or more per ml.

For the purpose of clinical classification those strains were classed as resistant, moderately or nearly susceptible, which showed 50 colonies or more at the above defined highest isoniazid concentrations. For the virulence experiments reported in this paper, those strains were only chosen, which showed the same degree of growth as the controls at the defined isoniazid concentrations viz. total or 100 per cent resistant, moderately or nearly susceptible.

Results:

I. *Growth in vivo.*

With many strains, isolated during isoniazid treatment, the resistance is combined with a gradual inhibition of growth on solid egg medium. Strains, growing eugonic before treatment, often represent an attenuated dysgonic growth during therapy, thus appearing as bovine strains. But after one or a few subcultures on egg medium they grow again eugonic and are not pathogenic for rabbits. Thus they cannot be considered as bovine strains, but they must be defined as human strains, which have become dysgonic.

This attenuation of growth is closely related with the isoniazid treatment. It is often observed at the first appearance of a resistant strain, and it may remain during the whole period of treatment or it may disappear slowly under continued treatment, and the strains may regain their normal eugonic growth in spite of their isoniazid resistance. Besides resistant strains have been isolated from patients which show normal growth more or less after the end of treatment. There are also cases with strains only moderately attenuated (moderately dysgonic) and also resistant strains, which always grow eugonic.

If there are only some resistant organisms in the culture, normal big colonies may be observed along with the dysgonic attenuated colonies. If they were picked up, the dysgonic colonies were resistant, whereas the colonies with normal growth frequently are susceptible to isoniazid. Similar observations are reported by *Courment, Galy and Deries* with streptomycin resistance.

II. *Study of Virulence with Guinea Pigs.*

Strains sensitive to isoniazid, streptomycin, para-aminosalicylic acid and conteben produce in the guinea pig a fair or severe generalized tuberculosis of all lymph nodes and internal organs. The severity of the disease is expressed by a high macroscopic index of 10-16 (Table I). If the guinea pigs are infected with great numbers of bacilli, the animals die early with a distinct, but not severe tuberculosis. By lowering the dose of infection, the duration of life increases and so does the severity of tuberculosis. The

macroscopic indices are therefore the highest with the animals, which have been infected with minimal numbers of bacteria.

Nearly all cultures of the different organs have become positive. The guinea pigs, infected with susceptible strains, therefore, have a cultural index of 6.2-7 (almost the highest possible), if 6-7 organs are cultivated. All but two guinea pigs died due to tuberculosis (Table I).

Strains, exclusively resistant to isoniazid (as determined by sensitivity tests of the primary culture as well as afterwards of all cultures of the different guinea pig organs) produce much lower indices (Tables II and III).

The guinea pigs, infected with *dysgonic isoniazid resistant* strains have an average macroscopic index of only 2.0 and a cultural index of only 1.8; that means, the animals have nearly no tuberculosis of the internal organs and only slight tuberculosis of the lymph nodes, tubercle bacilli may be cultivated only from a few organs or lymph nodes. The severity of tuberculosis depends on the dose of infection and on the duration of life. Smaller numbers of bacilli (0.0001-0.00001 mg.) produce generally no tuber-

TABLE I

GUINEA PIG EXPERIMENT WITH SUSCEPTIBLE STRAINS

Number of Strains of Mycobacteria Tuberculosis	Number of Guinea Pigs	Dose of Infection in Mg.	Average Duration of Life in Days	Average Tuberculous Index Per Animal	
				Macroscopic	Cultural
1	2	1.0	36	10.0	7
3	5	0.01	69	11.7	6.6
3**	6	0.0001	84	12.4	6.2
2**	3	0.00001	125	16.3	6.3
5*	16		80	12.6	6.6

*Some strains were examined with two or more infection doses.

**Two strains were cultivated from patients after one or two months of treatment with isoniazid, the rest was cultivated before treatment of the patients.

TABLE II: GUINEA PIG EXPERIMENT WITH DYSGONIC ISONIAZID RESISTANT STRAINS

Number Tuberculosis	Number of Guinea Pigs	Dose of Infection in Mg.	Average Duration of Life in Days	Average Tuberculous Index Per Animal	
				Macroscopic	Cultural
3	5	0.5-1.0	59	2.7	3.6
10	12	0.01	60	1.2	1.2
8	9	0.01	107	2.2	1.8
12*	26		76	2.0	1.8

*Most strains were examined with two doses of infection. Two other strains were examined with 0.0001 and 0.00001 mg. at six guinea pigs; the animals showed neither macroscopic nor cultural tuberculosis.

culosis, moderate numbers (0.01 mg.) produce slight tuberculosis of the lymph nodes, large numbers (1.0 mg.) were used only exceptionally, they produce only slight tuberculosis also, but the cultural indices are somewhat higher. Not a single guinea pig of this group died from tuberculosis.

Moderate dysgonic and eugonic resistant strains are increasingly more virulent (Table III). They produce for about the same average duration of life somewhat higher macroscopic and cultural indices, but these are much lower than those of the susceptible strains examined.

Moderate susceptible strains with eugonic growth at 1 mcgm. isoniazid per ml. egg medium behave similarly (Table III).

The same decrease of virulence was reported *(Meissner)* with the material from a section with cultures, in which there was found nearly 100 per cent double resistance to streptomycin and isoniazid (each bacterium resistant to both chemotherapeutics) (Table IV). The section material of two other patients (one with susceptible strains and the other with strains totally

TABLE III

GUINEA PIG EXPERIMENT WITH ISONIAZID RESISTANT STRAINS

Number of Examined Tuberculosis	Number of Guinea Pigs	Dose of Infection in Mg.	Average Duration of Life in Days	Average Tuberculous Index Per Animal	
				Macroscopic	Cultural
Moderately Dysgonic, Resistant:					
2	6	0.01-1.0	72	3.1	3.5
Eugonic, Resistant:					
4	9	0.01	88	4.8	3.7
Eugonic, Moderately Susceptible:					
1	3	0.001-0.01	98	5.3	4.3

TABLE IV

GUINEA PIG EXPERIMENTS WITH MATERIAL FROM SECTIONS

Cases With Susceptible and Resistant Strains

Quality of the Cultivated Strains	Number of Organs	Number of Guinea Pigs	Average Duration of Life in Days	Average Tuberculous Index Per Animal	
				Macroscopic	Cultural
Susceptible*	9	12	71	10.5	6.0
Resistant to Streptomycin**	6	10	85	13.5	7.0
Resistant to Streptomycin and Isoniazid***	12	15	75	3.5	3.5

*Patient died after 26 days' treatment with isoniazid.

**Patient died two years after treatment with streptomycin and one year after treatment with isoniazid.

***Patient died nine months after treatment with streptomycin and two months after treatment with isoniazid.

TABLE V

GUINEA PIG EXPERIMENT WITH STRAINS, CONTAINING A MIXTURE OF SUSCEPTIBLE AND RESISTANT MYCOBACTERIA

Number of Guinea Pigs	Dose of Infection in Mg.	Average Duration of Life in Days	Average Tuberculous Index Per Animal Macroscopic	Cultural
Strain Hell; 25 per cent Resistant to 10 Gr. Isoniazid, Dysgon:				
2	1.0	74	12.5	6.5
2	0.01	99	12.5	6.5
Strain Finke; Nearly 100 per cent Resistant to 10 Gr. Isoniazid, Eugon:*				
1	0.01	62	5.5	5.0
2	0.0001	79	4.0	4.0

*The susceptible bacteria showed growth at 0.1 gr. isoniazid, the strain is somewhat attenuated in its sensitivity.

TABLE VI: SENSITIVITY TESTS WITH STRAINS FROM GUINEA PIGS INOCULATED WITH A CULTURE, CONTAINING 25 PER CENT BACTERIA RESISTANT TO ISONIAZID

Strains From Guinea Pig Organs	Growth of Mycobacteria at the Following Concentration of Isoniazid in mcgr. 50	10	1.0	0.1	Control
Guinea Pig 9291, Infection with 0.01 Mg., Killed After 63 Days:					
Lymph node Ingual, Right	—	+	++	++	++++
Lymph node iliac	—	+++	++++	++++	++++
Spleen	—	±1*	±1	±2	++++
Liver	—	++	++	++	++++
Lungs	—	0	0	0	++
Guinea Pig 9292, Infection with 0.01 Mg., Killed After 135 Days:					
Lymph node Ingual, Right	0	0	0	0	++++
Lymph node Ingual, Left	0	0	0	0	++++
Lymph node iliac	0	0	0	0	++++
Spleen	0	0	0	0	++++
Liver	++	++	++	++	++
Lungs	0	0	0	0	++++
Lymph nodes paratracheal	0	0	0	0	++++

Sensitivity tests on solid egg medium (Hohn-Gottsacker).

The tubes were inoculated with one loopful of a suspension, containing 0.1 mg. mycobacteria per ml. normal saline.

+-++++ = growth as to the density.

± = single colonies, less than 10.

* = number of the single colonies.

TABLE 7

GUINEA PIG EXPERIMENT — INFECTION 0.01 mg. MYCOBACTERIA TUBERCULOSIS

MIXTURES OF SUSCEPTIBLE AND RESISTANT SINGLE COLONY CULTURES FROM THE SAME SPUTUM

RESISTANT MYCOBACTERIA	0%	10%	20%	50%	80%	90%	95%	98%	99%	100%
PARATRACHEAL NODES	SUSCEP.	SUSCEP.	SUSCEP.	SUSCEP.	25%	NEG.	NEG.	SUSCEP.	NEG.	100%
LUNGS	NEG.	NEG.	NEG.	NEG.	SUSCEP.	NEG.	SUSCEP.	NEG.	NEG.	NEG.
LIVER	SUSCEP.	SUSCEP.	SUSCEP.	10%	SUSCEP.	NEG.	100%	100%	NEG.	NEG.
SPLEEN	SUSCEP.	SUSCEP.	SUSCEP.	50%	NEG.	SUSCEP.	NEG.	100%	NEG.	100%
ILIAC NODES	SUSCEP.	SUSCEP.	SUSCEP.	LESS THAN 10%	25%	100%	50%	100%	NEG.	100%
INGUINAL NODES (RIGHT)	SUSCEP.	10%	25%	10%	100%	100%	100%	100%	50%	100%
INGUINAL NODES (LEFT)	SUSCEP.	SUSCEP.	SUSCEP.	SUSCEP.	25%	NEG.	50%	50%	SUSCEP.	100%
DURATION OF LIFE (DAYS)	22	21	22	22	21	9	14	21	47	47

RESISTANT MYCOBACTERIA = GROWTH AT 50 mcgm. 4 PLUS
SUSCEPTIBLE MYCOBACTERIA = GROWTH AT 0.1 mcgm. 4 PLUS ISONIAZID

resistant to 100 mcgm. streptomycin) produced high macroscopic and cultural indices.

If the examined culture contains a *mixture of resistant and susceptible bacteria*, the sensitive organisms determine the severity of tuberculosis in the guinea pig. With the same dose of infection and nearly the same duration of experiment many more organs showed macroscopic tuberculosis and nearly all organs gave positive cultures (Table V). All guinea pigs, infected with strain Hell., which had about 25 per cent bacteria resistant to 10 mcgm. isoniazid per ml. and about 10 per cent resistant ones to 50 mcgm. per ml., had high macroscopic and cultural indices, being characteristic for the susceptible strains in Table I. If the number of susceptible organisms is only small, as with strain Finke, the indices for about the same duration of experiment with the dose of infection of 0.01 mg. are indeed not much, but distinctly higher than a strain, which grows eugonic and is totally resistant. But even a hundredth part of this dose of infection (0.0001 mg.) produced fair tuberculosis in the lymph nodes, nevertheless the sensitivity of the susceptible proportion of mycobacteria is decreased slightly with growth at 0.1 mcgm. per ml.

III. *Sensitivity Tests of Separately Cultivated Strains of Different Guinea Pig Organs.*

In testing the cultures from each organ of infected guinea pigs for resistance to isoniazid, we found a *new criterion for the decrease of virulence: differences in the rapidity to spread in the guinea pig*. The mycobacteria, which acquired resistance to isoniazid in vivo, showed *a more delayed ability to spread (generalize) into the organs of the guinea pig* than the susceptible organisms of the same population. An example out of a great number of similar experiments is presented in Table VI. It deals with guinea pigs, infected with the strain Hell. (25 per cent resistant mycobacteria). The proportion of resistant strains in the different organs 63 days after infection differs; especially lungs and spleen show none or only a few resistant mycobacteria, whereas liver and lymph nodes have a larger proportion. The second guinea pig, infected with the same dose on the same day, presents after 135 days resistant organisms only in the liver, in all the other organs the number of resistant mycobacteria has become so small, that only susceptible ones are to be found in the test. If there are mixtures of resistant organisms and such, which are somewhat decreased in sensitivity, always the more susceptible organisms spread more rapidly than the resistant strains, also if the number of the more sensitive organisms was so small, that it was not definitely detectable at the routine sensitivity test of the primary culture.

IV. *Infection of Guinea Pigs with Artificial Mixtures of Susceptible and Resistant Mycobacteria.*

For these experiments we used single colony cultures of the same strain or of the same patient. The resistant cultures, tested each time after several subcultures on solid egg medium, were always found to be totally

(100 per cent) resistant. The virulence of such cultures, which have been subcultured four to six times, is somewhat greater, especially in larger doses, than that of freshly isolated resistant cultures. Table VII presents part of these experiments and contains one guinea pig from each of the mixtures of the mycobacteria: the guinea pig infected only with sensitive organisms has in each organ without exception susceptible germs, and in the guinea pig infected with resistant bacteria, there were recovered without exception only resistant strains. The guinea pigs inoculated with 10 and 20 per cent of the resistant culture show after 21 days a strain with a composition of mycobacteria corresponding to that of the injected mixture only in the lymph nodes of the site of injection. All cultures isolated from other organs were susceptible. The higher the proportion of the injected resistant organisms, the fewer is (within the short period up to 47 days) the number of organs with susceptible strains, but even from infection with emulsions containing 90 to 99 per cent resistant mycobacteria and corresponding only 10 to 1 per cent susceptible ones, there are guinea pigs, which contain at least in one organ, susceptible cultures without exception.

The cause of the disappearance of the resistant microorganisms in the guinea pig may be the more rapid multiplication of the susceptible strains, which, therefore, spread more rapidly and overrun the resistant ones, so that the latter cannot be detected in the test. We never have observed a change from resistant organisms into susceptible ones in the guinea pig, at least not at the first animal passage: 101 cultures isolated from the different organs of 20 animals which were infected with totally resistant strains from single colony cultures of two different patients (resistant control animals of the mixture experiments) were without exception totally resistant. These tests include six cultures from one guinea pig, which was killed 131 days after infection. Never was there found any susceptible mycobacterium.

Discussion.

Strains of mycobacterium tuberculosis resistant to isoniazid if cultivated freshly from sputum of patients during treatment and containing only resistant and no susceptible organisms, show, as first subculture, a lower virulence in the guinea pig than strains which are susceptible for isoniazid, streptomycin, para-aminosalicylic acid and conteben. Strains chosen under such conditions showed in no case the usual high virulence. These findings correspond to observations of Barry, Conalty and Gaffney; Peizer, Widelock and Klein as well as partly Steenken and Wolinsky, who observed loss of virulence of strains that were either made resistant to isoniazid in vitro or had become resistant in vivo. However these findings are not in accord with the observations of Tuczek and Saupe and Barnett, Bubshy and Michison, who never saw decrease of virulence in the guinea pig. Fust and Boehni observed such decrease only in a small proportion of their cases.

Our results on the more rapid spreading of susceptible mycobacteria in a population may give an explanation for the different observations of other workers. If there are not tested *afterwards* the separately isolated

cultures of the different guinea pig organs and found to be totally resistant, there remains the possibility that susceptible organisms are not recovered in the injected culture. *In these cases there are the susceptible mycobacteria which have produced tuberculosis of the guinea pig organs, but not the resistant ones.* Without testing afterwards the different organ cultures it is only possible to examine the virulence of the given culture, but it is impossible to prove that it is only the virulence of the resistant organisms contained in the population, that has been tested. Also the question if guinea pigs which are infected with sputum containing isoniazid resistant mycobacteria may be influenced by treatment with isoniazid (Tuczek and Saupe), can only be decided if sensitivity tests of all organ cultures of the untreated control animals have shown that the injected sputum contained only resistant, but not susceptible microorganisms. Smaller numbers of susceptible germs may only be detected by sensitivity tests on solid medium with small inocula, but not in liquid medium. The experiment with guinea pigs is, under suitable conditions, a more sensitive agent to detect isoniazid susceptible mycobacteria in a population than the sensitivity test in vitro.

In agreement with Fust and Boehni we would like to conclude that it may be permitted to use for sensitivity tests such cultures which are recultivated from guinea pig organs when the culture from the original material remained negative. It is suitable to kill the animals eight weeks after infection at the latest and to cultivate only the tissues at the site of injection or the lymph nodes on the side of injection. The more distant from the place of infection the organs are and the longer the guinea pigs survive, the greater is the probability that existing possibly susceptible bacteria change the sensitivity picture of the guinea pig culture to the susceptible side in contrast to the bacterial composition of the original material. We observed the same with subcultures in vitro. Therefore we consider that sensitivity tests should be carried out from the primary culture, but not from further subcultures.

The more rapid multiplication of the susceptible mycobacteria may be the cause for the decrease of resistance which sometimes appears in patients after termination of treatment. Our experiments with single colony cultures allow us to conclude that the single bacterium maintains its resistance, but that the resistant ones were overrun by the susceptible, more rapid multiplying bacteria of the same population.

We are of the opinion that fresh disseminations and fresh lesions are produced by susceptible bacteria, because the latter multiply more rapidly and evoke more severe tuberculous lesions in the living organisms. Thus we may explain the good recovery of patients with these forms of tuberculosis by repeated treatment with isoniazid, also in cases with resistant strains in some cavities of the lungs.

As there are all degrees of decrease of growth and virulence with isoniazid resistant strains, there may also exist strains with so great an attenuation that they fail to be cultivated in vitro or to infect the guinea pig or that they fail to be detected in both experiments.

The experiments were continued especially with regard to the examination of a greater number of strains with different degrees of decreased susceptibility, and to the constancy of the attenuation of virulence in vivo and in vitro.

SUMMARY

1) Tubercle bacilli strains susceptible to isoniazid, streptomycin, para-aminosalicylic acid and conteben (5 strains, examined in 16 guinea pigs) produce in the guinea pig generalized tuberculosis of lymph nodes and internal organs. As an expression of the severity of tuberculosis is to be observed a high macroscopic (10-16) and a high cultural (6-7) tuberculous index at an average survival time of two to three months. These indices mean the sum of the macroscopic numbers for the different organs and the sum of the organs with positive cultures.

2) Strains resistant to isoniazid, recovered from patients during treatment with isoniazid (21 strains examined in 56 guinea pigs) produced at the examination of the first egg medium subculture with a medium dose of infection (0.01 mg.) and in the same period only minimal tuberculosis of lymph nodes and practically no tuberculosis in the organs and, corresponding to this finding, only a small number of positive organ cultures. At the highest degree of virulence attenuation, which is combined with a distinct attenuation of growth on egg medium, there were observed macroscopic and cultural indices of 1.6 and 1.9.

3) The attenuation of virulence decreases somewhat, changing from the moderately dysgonic resistant strains via the eugonic resistant ones to the moderately susceptible eugonic strains, but their indices (the latter have such of 5.3 and 4.3) are distinctly much lower than those of our susceptible strains.

4) To demonstrate the attenuation of virulence it must be supposed, that only strains were examined, which contain without exception resistant mycobacteria, but not susceptible or more susceptible ones.

5) If guinea pigs are infected with cultures containing mixtures of resistant and susceptible mycobacteria or with artificial mixtures of susceptible and resistant single colony cultures, the susceptible organisms spread (generalize) more rapidly than the resistant ones of the same population.

6) Experiments with single colony cultures indicate that the single bacterium does not lose its resistance in the guinea pig, at least not in the first animal passage. The cause of the more rapid generalization may be the more rapid multiplication of susceptible bacteria in contrast to the resistant ones of the same population in the animal.

RESUMEN

1) Las cepas de bacilo de la tuberculosis susceptibles a la isoniacida, estreptomicina, PAS y Conteben (5 cepas examinadas en 16 cuyes), producen en el cuy tuberculosis generalizada de los ganglios linfáticos y de los órganos internos. Como una expresión de la tuberculosis es de observarse un índice elevado macroscópico (10-16) y un alto índice cultural (6-7) con

tiempo de sobrevida medio de dos a tres meses. Estos índices corresponden a la suma de los números microscópicos para los diferentes órganos con cultivos positivos.

2) Las cepas resistentes a la isoniacida, obtenidos de enfermos durante tratamiento con isoniacida (21 cepas examinadas en 56 cuyes) producidas al examen del primer medio de huevo en subcultivo con una dosis media de infección (0.01 mg.) y en el mismo período causaron tuberculosis mínima de los ganglios y no produjeron prácticamente tuberculosis de los órganos y correspondiendo a este hallazgo, sólo produjeron un pequeño número de cultivos positivos de órganos. En el grado más elevado de atenuación de la virulencia, que es combinada con clara atenuación del crecimiento en medio de huevo, se observaron índices macroscópicos y culturales de 1.6 y 1.9.

3) La atenuación de la virulencia decrece algo cambiando de las formas resistentes moderadamente disgónicas hacia las formas resistentes eugónicas hasta las cepas eugónicas moderadamente susceptibles, pero sus índices (el último tiene tales como 5.3 y 4.3) son claramente mucho más bajos que los de las cepas susceptibles.

4) Para demostrar la atenuación de la virulencia, debe suponerse que sólo se examinaron cepas que contienen sin excepción micobacterias resistentes, pero susceptibles o algunas más susceptibles.

5) Si los cuyes son infectados con cultivos que contienen mezclas de micobacterias resistentes y susceptibles o con mezclas artificiales de cultivos simples susceptibles y resistentes, los organismos susceptibles se diseminan (generalizan) más rápidamente que las resistentes de la misma población.

6) Los experimentos con cultivos de colonia simple, indican que el bacilo de esos cultivos simples, no pierde su resistencia en el cuy, por lo menos, no en el primer paso en el animal. La causa de la más rápida generalización, puede ser la más rápida multiplicación de las bacterias susceptibles, en contraste con las resistentes de la misma población, en el animal.

RESUME

Les souches de bacilles de Koch sensibles à l'isoniazide, à la streptomycine, au P.A.S. et au "conteben" (5 souches examinées chez 16 cobayes) provoquèrent chez les cobayes une tuberculose généralisée des ganglions et des viscères. A noter, comme signe de la gravité de la tuberculose, un index tuberculeux élevé à l'examen macroscopique (10-16) et à la culture (6-7) pour une survie moyenne de deux à trois mois. Les index sont calculés en additionnant le nombre des organes atteints de tuberculose macroscopique et le nombre de viscères donnant lieu à des cultures positives.

2) Les souches résistantes à l'isoniazide, obtenues à partir de malades en cours de traitement par l'isoniazide (21 souches examinées chez 56 cobayes) ne provoquèrent que des tuberculoses discrètes des ganglions et pratiquement aucune localisation viscérale. En accord avec ces constatations, il n'y eut qu'un petit nombre de cultures de viscères qui se montrèrent positives. A son plus haut degré d'atténuation de la virulence, on observa

des index macroscopiques et de cultures de 1.6 et 1.9. Ces constatations se trouvaient associées à une atténuation très nette des possibilités de cultures sur milieu à l'oeuf.

3) Il y eut une certaine décroissance de l'atténuation de la virulence, transformant les souches résistantes modérément dysgoniques en souches modérément sensibles, de caractères, eugoniques, en passant par l'intermédiaire de souches résistantes à caractères eugoniques. Toutefois, leurs index (dans le dernier cas, il était de 5.3 et 4.3) étaient nettement plus bas que ceux des souches sensibles que nous avons étudiées.

4) La démonstration de l'atténuation de la virulence suppose que furent examinées seulement les souches qui ne comportaient que des germes résistants, et en aucun cas des bacilles plus ou moins sensibles.

5) Si des cobayes sont infectés par des cultures qui contiennent un mélange de germes résistants et de germes sensibles ou par les cultures d'une seule colonie de germes sensibles et de germes résistants artificiellement mélangés, on assiste à une diffusion beaucoup plus rapide des germes sensibles que des résistants appartenant à la même population.

6) Les expériences établies avec la culture d'une seule colonie montrent que dans ce cas les germes ne perdent pas leux résistance chez le cobaye et en tout cas lors du premier passage. Il est possible que la raison de la génération accélérée des bacilles sensibles soit due au fait que leur multiplication est plus rapide, à l'opposé de ce qui se passe chez l'animal pour les souches résistantes de la même population.

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Endomyocardial Fibroelastosis*

A Study of Thirty Cases

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Subsequent to the definitive studies of Craig,[1] Pryor and Wyatt,[2] and others, endomyocardial fibroelastosis has been recognized as a distinct pathological entity even though certain details are not yet fully clarified. Several recent papers[2-6] have brought knowledge of its clinical aspects to the point where it is almost as well defined clinically as pathologically. At first glance, it might seem that the least standardized facet of this syndrome is the nomenclature, for, among other terms, it is variously described as endocardial sclerosis or dysplasia, subendocardial sclerosis or fibrosis, endomyocardial fibrosis or fibroelastosis, depending, apparently, upon the author's concept of the basic pathological process, which is not at all uniform or precisely defined. For the same reason, the last term will be used in this paper, in accord with the concept that the disease consists of a diffuse or focal thickening of the endocardium and the subendocardial myocardium, consisting predominantly of fibrous and elastic tissue. This is especially in accord with the concepts of Johnson.[6]

Study of those cases which have come to autopsy at Children's Hospital (Denver), however, has led to the recognition of certain concepts which have apparently not been described in print, and others which have only just been recognized. This paper represents a study of the 30 cases discovered during the five year period ending April 30, 1952. The annual incidence curve resembles a logarithmic progression, indicating that this probably does not represent the total incidence in the earlier years of the period. Still earlier records, while yielding an occasional obvious case, are too incomplete to be of real value, especially since this disease was not then sought by the prosectors. The gross and microscopic pathology of all dubious cases were rechecked as closely as possible; the few in which this could not be satisfactorily accomplished are fully discussed in the appropriate section below.

All cases in this study, with two exceptions, were diagnosed on the basis of the microscopic criteria of Craig,[1] and Pryor and Wyatt.[2] No microscopic examination is available on these two cases. One of these (A48-2) is among the earliest of the series, and occurred at the time when interest in the entity was just developing. Grossly, it is a totally typical example of the atrio-ventricular valvular type of the disease as previously designated. The valves were described as follows: "The mitral and tricuspid valves are poorly developed. The mitral lacks chordae tendinae and papillary muscles. The edge of the tricuspid valve is nodular."

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The other case (A52-7) is recent, and the section was apparently overlooked in error, leaving the specimen regrettably open to question. The opinion of the experienced prosector, however, was that this case represented "hypoplasia of the left auricle with endomyocardial fibroelastosis." While it might at first seem atypical to find this process in the hypoplastic instead of the hypertrophied or dilated chamber, examination of Craig's and Johnson's cases reveal several with small chambers, some of which are quite comparable to this example. Elsewhere in this series are two rather similar cases. We have therefore felt justified in including these cases.

The cause of endomyocardial fibroelastosis is a truly debatable subject. Originally known as "fetal endocarditis" from the gross appearance of the valves, it was soon recognized that even in premature infants the pathologic picture is not inflammatory,[5] and the older concept and nomenclature were abandoned. There appears to be a wide variance of opinion as to the etiology, mostly based, unfortunately, upon greatly limited material. Hill and Reilly,[7] on the basis of one case, suggest that this may be a collagen disease. This also appears to be the belief of Becker, Chatgidakis and Van Lingen,[8] but since their age distribution and pathologic discriptions vary so markedly from the others in the literature, it cannot be presently concluded that their "cardiovascular collagenosis with parietal endocardial thrombosis" is the same disease entity under discussion here. Stadler, Reid and Friedman[9] have reverted to the older theory of inflammation, again on the basis of a single case, which, however, seems to resemble the microscopic appearance of rheumatic fever to some degree. Because the pathology of this disease often simulates that of an infarct, it has long been considered that anoxia plays a major part in the production of the fibroelastosis. Johnson[6] has recently advanced the theory, based on the study of 210 congenital hearts showing evidence of endomyocardial fibroelastosis, that all these cases are due to anoxia, either as the result of certain anomalies of the coronary arteries, of premature closure of the foramen ovale, or of stagnation anoxia in the case of atretic valves or chamber. Since his is by far the largest series, considerable attention must be devoted to his conclusions. The majority of authors at present agree fairly well that the basic pathology is congenital, and should be considered together with other idiopathic congenital anomalies. Previous evidence has been introduced[1] from studies of twins that this disease process is the result of changes occurring during development, rather than a basic ovular defect. We have no information either positive or negative, concerning the role of maternal infection in the cases in this series.

In view of the excellent and well-known studies of Prior and Wyatt[2] and of Craig et al.,[1] it seems hardly justified to devote time to a detailed description of the pathologic anatomy of this disease process other than that given in the tabulated cases.

It becomes apparent upon close study, however, that especially in the valvular types there is yet unexplored ground. Some of the cases in this and other series are characterized by rolled, nodular valve margins, while

others are diffusely thickened and hypoplastic. Similarly, upon microscopic examination, some show a simple diffuse fibrosis of the leaflet. The literature has provided no clue as to the proper division of these types, and the apparent intergradation of cases in this series has tended to confuse rather than clarify. Nevertheless, we have excluded, perhaps arbitrarily, one case (A52-9) of isolated valvular pulmonic stenosis (with auricular septal defect) which showed simple fibrosis of the valve on autopsy at 15 months and was at first felt to represent the entity under discussion. Within a short time, however, we observed a remarkable series of isolated valvular pulmonic stenoses of varying degree, climaxed by three cases of total valvular atresia, which showed no nodularity and a microscopic pattern of simple fibrosis. We therefore feel justified in assigning A52-9 to this last group rather than to the proven endomyocardial fibroelastosis, despite the lack of any recognition of such grouping evident in the literature. Indeed, from a study of the literature alone, one would hesitate not to include nearly all the cases of isolated valvular pulmonic stenosis with the valvular group of endomyocardial fibroelastosis.

It now seems generally accepted, as apparently first suggested by Gross,[10] that the infarct-like myocardial changes and the dilatation of the subendocardial vessels are the secondary results of the occlusion of arterioluminal, arteriosinusoidal and Thebesian vessels as the result of the fibroelastotic process, and several of our cases have this distinct appearance. Johnson has summarized considerable research with the conclusion that only in late fetal life do the coronary arteries take over the function of supplying the endocardium and subendocardium from these lesser-known vessel systems. As previously mentioned, it is his conclusion that the pathogenesis in this disease is entirely the result of local fetal anoxia. For reasons to be discussed below, however, it is our belief that judgement must be reserved pending additional studies.

In practically all major series reported to date, anomalies of coronary circulation have received considerable attention because of their possible role in the production of anoxia. Despite the shifting of emphasis from the coronary circulation to that of the arterioluminal and related systems, the anomalies encountered in this group are listed in Table I. It is obvious

TABLE I

ANOMALIES OF CORONARY FLOW

1. *Anatomical Anomalies:*		
*A48-4	No right coronary artery.	EMF of mitral and tricuspid.
A48-54	Coronaries arise together.	EMF of left ventricle.
*A52-7	High takeoff.	EMF of left auricle and tricuspid.
A52-13	High takeoff.	Both auricles.
*A52-24	High takeoff.	Left ventricle and aortic valve.
2. *Anatomicophysiological Anomalies:*		
*A50-18	Atresia of aortic valve.	Both ventricles.
*A51-46	Atresia of aortic valve.	Left ventricle and mitral.

*Other major cardiovascular anomalies present.

from examination of this data that none of the anomalies could have caused focal anoxia of the areas of coexistant endomyocardial fibroelastosis. In particular, none arose from the pulmonary artery.

It has often[1,2] but not always[7] been stated that endomyocardial fibroelastosis is primarily a disease of the left side of the heart. The involvement of the various chambers and valves in this series is given in Table II. These figures appear to represent a somewhat higher incidence of right sided lesions than is usually stated, but due to the fact that the majority of these occur in diffuse cases, this is more apparent than real. As seen in Table IV, only four are purely right sided, while eight are limited to the left side of the heart.

Many of the series in the literature stress the lack of association of endomyocardial fibroelastosis with other congenital abnormalities, either of the cardiovascular or other systems. This was strikingly untrue of this group in which 75 per cent show associated abnormalities. As shown in Tables IV and V, 11 cases (36 per cent) were associated with significant non-cardiovascular anomalies, and 17 (57 per cent) with anomalies of cardiovascular nature, although in the latter group no attempt has been made to exclude physiologically patent foramen ovale and ductus arteriosus. As can be seen, several cases show anomalies of both types. In 16 cases (53 per cent) the clinical aspects are overshadowed or completely hidden

TABLE II: TOTAL INCIDENCE OF ENDOMYOCARDIAL FIBROELASTOSIS IN EACH CHAMBER AND VALVE

	No.	Pct.		No.	Pct.
Left auricle	13	43	Right auricle	11	36
Left ventricle	21	70	Right ventricle	15	50
Mitral	14	47	Tricuspid	9	30
Aortic	9	30	Pulmonic	5	17

TABLE III

AREAS OF OCCURRANCE OF ENDOMYOCARDIAL FIBROELASTOSIS

4 chambers and 4 valves	3
4 chambers and 1 valve (2 mitral, 1 aortic)	3
Both ventricles and both atrioventricular valves	2
Both ventricles	3
Both ventricles and both auricles	2
Both auricles	1
Both atrioventricular valves	1
Left ventricle	2
Right ventricle	2
Left auricle, ventricle and atrioventricular valve	2
Right auricle, ventricle and atrioventricular valve	1
Left ventricle and valves (Both, 1; M, 1; A, 1)	3
Left auricle and ventricle	1
Pulmonic	1
Aortic, mitral and pulmonic	1

by the severe concomitant anomaly. The anomalies present in the other six cases of the 22 are not believed of major clinical importance. As has been pointed out elsewhere,[1] abnormalities of the papillary muscles and associated valvular structures appear to be a common integral part of this disease, and therefore, have not been included among the associated anomalies.

It is evident from examination of this data that there is no direct

TABLE IV: NON-CARDIOVASCULAR ANOMALIES ASSOCIATED WITH ENDOMYOCARDIAL FIBROELASTOSIS

A48-92	Right cryptorchism.
*A48-4	Deformities of 1st fingers and 3rd toes.
	Deformities of right foot.
	Deformities of hip and knee joints, skull and sacrum.
	Maldevelopment of left kidney and urethra.
	Hypoplasia of right kidney.
	Malrotation of intestines.
A48-54	Hemangioma of vulva.
	Mental deficiency.
A49-72	Globus cell masses of brain.
A49-97	Microglial proliferation of hindbrain, probably congenital.
**A50-18	Hypospadius.
	Diverticulum of gall bladder.
A50-90	Mucoviscidosis.
**A50-98	Pyloric stenosis.
A51-51	Reduplication of ureters.
**A52-7	Diverticulum of pylorus.
A52-13	Ecchondroses of rib junctions; multiple lesions of cerebral palsy.

*Minor additional cardiovascular anomaly present.
**Major additional cardiovascular anomaly present.

TABLE V

SUMMARY OF CO-EXISTING CARDIOVASCULAR ANOMALIES

1. Aortic anomalies	11
Coarctation	(7)
Hypoplasia	(4)
2. Bicuspid valves	6
Disproportionate cusp	1
3. Atresia of aortic valve	2
4. Malrotations	3
5. Hypoplasia of ventricle	2
6. Hypoplasia of auricle	1
7. Tetralogy of Fallot or variant	3
8. Other significant ventricular septal defects	2
9. Significant venous anomalies	2
10. Patent foramen ovale or auricular septal defect	8
11. Patent ductus arteriosus	9
12. Patent foramen ovale and ductus arteriosus	(5)
13. Coronary arteries listed separately	

evidence of relationship between the presence of endomyocardial fibroelastosis and any specific anomaly, or anomalies of any system. A contrast is demonstrated, however, between the total incidence of associated anomalies in this series and in most of those reported elsewhere,[1-3] though this tendency has by no means been universal.[5,6] An interesting speculation arises, however, from the high percentage of associated coarctations of the aorta, hypoplasias of the aorta and hypoplasias of a cardiac chamber, which in part corresponds with the findings in Johnson's series. While this may well be mere coincidence in this small series, if the same phenomenon continues to be apparent in other series, it would be worthy of further investigation.

As has been mentioned, of the 30 cases in this series, in 16 the cause of death was an associated cardiovascular anomaly. Of the remaining cases, four died of intercurrent illness without evidence of their cardiac disease, one died during an attempt at surgical correction of the physiological anomaly, and the other nine as the direct result of this syndrome. The clinical picture of the groups thus outlined is widely divergent, and thus it has seemed proper to approach them from different standpoints.

Since the cases in which other cardiovascular anomalies mask the clinicopathological significance of the entity under discussion are primarily of investigational interest, the pertinent data on each of the cases with cardiovascular anomalies is listed in Table VI. The anomaly, the age at death, the sex and the areas of endomyocardial fibroelastosis are summarized. Also stated is the relative importance of the anomaly and the presence of noncardiovascular anomalies, which may thus be correlated with Table V.

Table VII summarizes the findings in cases whose death was unrelated to the cardiovascular system. Included for investigational purposes is a listing of the distribution of the endomyocardial fibroelastosis, associated anomalies, major pathology at death, and previous evidence of cardiac disease. These cases are of interest because of the relatively great longevity without clinical evidence of the disease. It might be held that case A51-120 died of secondary infection, but we have felt that the absence of previous evidence of heart disease indicated that this should be considered an unassociated disease, and the significance of the case is not dependent upon the nomenclature. It should be noted that there seems little correlation between the location and pathologic severity of the disease and the clinical course, in the other groups as well as this one.

Table VIII attempts a clinicopathological correlation of the 10 cases whose death was immediately due to the disease process under consideration. Included is the sex, age at death, distribution of the fibroelastosis, gross and microscopic data, associated anomalies, significant history, pertinent clinical and laboratory findings, and a brief summary of the course of the patient after discovery of the illness.

Several of the cases associated with other major cardiovascular anomalies, as shown in Table VI, are worthy of brief discussion. Despite his other major handicaps, Case A50-101 is the longest survival in our series,

TABLE VI

A47-82 Coarctation, disproportionate valve cusp (aortic).
(4 month male, left ventricle and mitral).

†A48-4 Bicuspid pulmonic valve, patent foramen ovale and ductus arteriosus, absent right coronary artery.
(4 month female, mitral and tricuspid).

A48-37 Bicuspid, stenotic aortic valve, coarctation, auricular septal defect.
(7 week female, mitral and tricuspid).

†A50-18 Hypoplasia of left ventricle and ascending aorta with aortic valve atresia and mitral stenosis, patent ductus arteriosus and foramen ovale.
(2 week male, right ventricle. Left ventricle saved intact, therefore uncertain).

*A50-88 Patent foramen ovale.
(surgical death at 4 years, male, 4 chambers and valves).

†A50-98 Coarctation.
(2 month female, both ventricles, mitral and tricuspid).

A50-101 Coarctation, bicuspid aortic and tricuspid valves, patent ductus arteriosus, multiple venous anomalies.
(20 year old male, both ventricles).

A50-107 Coarctation, patent ductus arteriosus.
(9 month male, left ventricle).

A51-5 Overriding aorta, bicuspid pulmonic valve, pulmonary artery hypoplasia.
(13 month female, infundibulum).

A51-13 Coarctation, patent ductus arteriosus.
(11 day female, 4 chambers).

A51-46 Hypoplasia of left ventricle with aortic valvular atresia, hypoplasia of aorta, patent foramen ovale and ductus arteriosus.
(5 day male, left ventricle and mitral).

†*A51-51 Patent foramen ovale.
(2 month female, 4 chambers and 4 valves).

†*51-60 Patent foramen ovale.
(4 week male, 4 chambers and aortic valve).

A51-70 Overriding aorta, right aortic arch and descending aorta, associated arterial anomalies.
(16 month female, infundibulum).

A51-75 Overriding aorta, right aortic arch and descending aorta, associated arterial anomalies, infundibular stenosis and bicuspid pulmonic valve.
(2 year old male, pulmonic).

A52-7 Hypoplasia of left auricle, mitral atresia, multiple ventricular septal defects, hypoplasia of aorta, bicuspid aortic valve, incomplete rotation.
(6 day male, left auricle and tricuspid).

A52-10 Partial transposition, ventricular septal defects, patent foramen ovale and ductus arteriosus, multiple venous anomalies.
(1 day male, left ventricle and aortic).

A52-23 Transposition with overriding pulmonary artery, coarctation, patent foramen ovale and ductus arteriosus.
(19 month male, 4 chambers and 4 valves).

* Associated anomaly not considered of primary clinical significance.
† Also major non-cardiovascular anomaly.

TABLE VII

SUMMARY OF FINDINGS IN CASES DYING OF UNASSOCIATED DISEASE

No.	Sex	Age	EMF Distribution	Assoc. Anom.
A50-92	F	10y	4 chambers	None
Pathology: Acute poliomyelitis, aspiration pneumonia.—Mild intramyocardial fibrosis with thicker plaques of endomyocardial fibroelastosis. *Previous Cardiac Signs, etc.:* None.				
A50-90	M	7y	Both ventricles	None *(Except, see Pathology)*
Pathology: Generalized fibrocystic disease with cystic duct atresia.—Smooth, shiny endocardium. Subendocardial fibrosis is seen especially in the papillary muscle bundles. *Previous Cardiac Signs, etc.:* Cor pulmonale and digital clubbing, probably related to the mucoviscidosis.				
A51-120	M	6m	Right auricle, ventricle and tricuspid	None
Pathology: Aspiration pneumonitis, lipoid and yeast.—Marked subendocardial thickening by fibrous and elastic tissue. The endocardium is china-white. The vessels in the subendocardial myocardium are dilated and the walls are thickened. *Previous Cardiac Signs, etc.:* Cyanotic last two days.				
A52-13	M	4y	Both auricles	Multiple ecchondroses, high take-off of coronary arteries
Pathology: Thrombotic occlusions of right internal carotid and left lenticulostriate arteries. Intiral sclerosis of common carotids. Encephalomalacia of right cerebrum and left thalamus. Lobar sclerosis of left parietal and right temporal lobes.—The endocardium of the left auricle is yellow-white and opaque. Microscopically, the right auricle is also involved, but to a lesser degree. *Previous Cardiac and Signs, etc.:* Grade II basal blowing systolic murmur. Cyanotic day of death.				

and perhaps the longest recorded to date, although endomyocardial fibroelastosis in adults may have been recorded under another name.[8,12] That his endomyocardial anomaly was by no means minimal may be judged from the following description in the original autopsy protocol: "The endocardium is thickened and milk-white, especially in the left ventricle . . . There is veil formation of the chordae tendinae in the mitral and tricuspid valves . . . (microscopically) there is marked subendocardial fibrosis with extention into the myocardial interstitium."

Three of these cases are in association with hypoplastic chambers, which is a small fraction of the total number of such malformations examined during this period. Case A50-18 showed hypoplasia of the left ventricle which was saved intact as a museum specimen. The endocardium of the right ventricle showed a patchy fibrous thickening interpreted as a mild form of the entity under discussion. Case A51-46, with hypoplasia of the left ventricle, showed, to quote the original protocol, "a few areas of sub-

TABLE VIII: CLINICOPATHOLOGICAL SUMMARY OF CASES DYING OF ENDOMYOCARDIAL FIBROELASTOSIS

No.	Age	Sex	Associated Anomalies
A47-92	19h	M	Patent ductus arteriosus, right cryptorchism.

Description: Very marked firm diffuse pinkish-yellow nodular thickening involving the full extent of the aortic and pulmonary valves. The surfaces are endothelialized and glisten. The valves appear as thick warty projections into the lumen. The individual cusps are marked by deep crevices in the thickened valves. Micro-overgrowth of subendothelial connective tissue.

Clinical Summary: Cyanotic and hyperpneic from birth with generalized edema, pulmonary, hepatic and splenic congestion. 300 cc. removed by paracentesis from abdomen. Died without response to oxygen, stimulants, etc.

A48-54	17m	F	No right coronary orifice, hemangioma of vulva, mentally deficiency.

Description: The endocardium of the left ventricle is a striking china-white. Micro-marked subendocardial sclerosis, marked dilatation of venules.

Clinical Summary: Mentally and physically retarded from birth with repeated respiratory infections, dermatitis and anemia. Liver 2 cms. below costal margin, grade I apical systolic murmur. Dyspnea increased terminally, became cyanotic and expired 12 hours after final illness began. Heart was seen to be large on x-ray film.

A49-72	5w	M	Globus cell masses of brain, mild hypoplasia, aortic valve.

Description: The endocardium of all 4 chambers is thickened by fibrous connective tissue. The arteriolar adventitia is also thickened. The septae between the myocardial bundles are thickened and the connective tissue content is increased. The mitral valve is stenotic but no sections of the valve were made.

Clinical Summary: Well for 2 weeks, then transient cyanosis, hyperpnea and vomiting. P 150, R 150, R 65, liver down 6 cms. Heart was generally enlarged by x-ray film and there was patchy pulmonary density. Improved until 4 days before death on antibiotics and oxygen, then became cyanotic and died during a push-in transfusion.

A49-97	13m	F	Proliferation of microglia, hindbrain.

Description: All chambers show a white glistening firm thick surface. There is minimal thickening of the peripheral cusp of the mitral valve. Micro—there is proliferation of a thick dense fibrous tissue which approaches hyalinization. Some fingerlike projections reach down into the underlying muscle to encircle muscle bundles. There is thickening of the vessel walls in the endocardium and subendocardium.

Clinical Summary: Repeated admissions with recurrent cyanosis and congestive failure; improved with supportive care. Terminal anasarca, cyanosis, hepatomegaly. A2 greater than P2. X-ray film showed vascular lung fields left auricular, and perhaps left and right enlargement. Rapid deterioration without response terminally.

A50-75	20d	F	None.

Description: Endocardium of all 4 chambers is thickened and milk-white. The right ventricle is the most involved. The subendocardial collaginous tissue is increased on microscopic examination.

TABLE VIII (Continued)

No.	Age	Sex	Associated Anomalies

Clinical Summary: Well for 2 weeks, then sudden onset of cyanosis, pallor, abdominal pain, vomiting and dyspnea. The heart was enlarged to the left; no murmurs heard. Terminal hepatomegaly. EKG—right ventricular hypertrophy. X-ray film: generalized cardiac enlargement, and increased pulmonary vascularity. The clinical diagnosis of endomyocardial fibroelastosis was made. There was no response to digitalis, oxygen and supportive measures.

A50-88 4y M Patent foramen ovale.

Description: The entire endocardium is smooth, shiny irregular and whitish. There is marked stenosis of the pulmonic valve and a similar yellowish-white but less stenotic thickening of the other valves. It is irregular and the cusps are fused. There is marked subendocardial, and moderate intramyocardial fibrosis.

Clinical Summary: Murmur noted at 6 weeks. Activity limited by dyspnea. Frequent respiratory infections. Alert, WD and WN. Lips cyanotic. Heart enlarged with loud harsh systolic murmur and thrill at the pulmonic area. Angiograms: large right auricle and ventricle, pulmonary artery small and slow-filling. Auricular septal defect present. Moderate delay in left ventricular emptying. Expired in surgery before pulmonary valvulotomy could be performed.

A50-113 10w M None.

Description: The left auricle is dilated and the endocardium is thick and yellow-white. The left ventricle is markedly dilated, the endocardium is thick and milk-white. The papillary muscles are irregular and mottled yellow. The mitral valve shows fine translucent beading at the attachment of the chordae tendinae. The inner half of the left ventricular myocardium is of increased density and yellow-white. The aortic valve is markedly distorted with numerous spheroidal white shiny excrescences up to 2 mm. in diameter projecting from all cusps. The subendocardium and the adjacent interstitial myocardium show a marked increase in fibrous and elastic tissue. The subendocardial arterioles are thickened and dilated.

Clinical Summary: Became cyanotic at 2 days. Improved with oxygen but continued to be cyanotic with crying. A systolic murmur was present. Liver and spleen enlarged. Heart greatly enlarged by x-ray film, with normal pulmonary vascularity. Dyspnea worsened, and infant became critical and failed to respond to oxygen, digitalis or supportive measures.

A51-51 2m F Patent foramen ovale, duplication of ureters.

Description: The endocardium of all the chambers is smooth, glistening, opaque and china-white, most prominently in the auricles and the areas of the ventricles adjacent to the valves. The myocardium is of increased consistency. All the valves but especially the mitral and tricuspid are somewhat thickened and opaque and white. Micro—the endocardium is moderately thick. Subendocardial collaginous and elastic tissue is increased. The myocardium is moderately hypertrophied. The myocardial vessels are distended and the walls of those in the subendocardium are thickened.

Clinical Summary: Mild cyanosis when crying with slow progression. No murmur or hepatomegaly found. Suddenly became deeply cyanotic and died en route to hospital.

TABLE VIII (Continued)

No.	Age	Sex	Associated Anomalies
A51-60	4w	M	Auricular septal defect.
Description: The endocardium of all the chambers is thickened and the myocardium is also increased in diameter. Micro—the endocardium is thickened by a layer of fibrous tissue which does not appear to extend into the underlying myocardium but involves the aortic valve.			
Clinical Summary: Cyanosis and murmur were noted at birth, but not again until 24 hours before death, when edema, cyanosis and dyspnea developed. A grade II-III diffuse systolic murmur was noted. The heart was enlarged to percussion. EKG: marked right axis deviation. X-ray film: lung fields clear, diffuse enlargement of heart. Congestive failure progress despite oxygen, digitalis, diuretics, etc.			
A51-114	4m	M	None.
Description: The endocardium of the left auricle and the superior portion of the left ventricle is china-white. The mitral valve is thickened and china-white. Micro—the subendocardial vessels show moderate thickening and dilatation in the areas of subendocardial fibroelastosis, especially in the auricle.			
Clinical Summary: Apparently normal, found dead in bed.			

endocardial sclerosis," in the wall of that chamber, thus apparently indicating a coexistance of pathology rather than suggesting that the hypoplasia was due to this entity. Case A52-7, with hypoplasia of the left auricle, has been previously discussed.

Three of this group are associated with pulmonic stenosis. Two of these cases (A51-5 and A51-75) are anatomically identical with or very similar to type 2 of Brock,[11] while the third (case A51-70), while similar, fails to posess its typical bicuspid pulmonic valve and hypoplastic pulmonary artery. Thus all three show infundibular stenosis as a part of the anatomical syndrome. Two of these (cases A51-5 and A51-70) show "distinct subendocardial sclerosis" of the infundibulum, the third does not. On the other hand, it shows coexistantly a valvular pulmonic stenosis, and the valve, upon microscopic examination, shows whorls of fibrous tissue of varying density together with diffuse fibrocytosis, a pattern commonly seen in certain cases of valvular endomyocardial fibroelastosis. As mentioned, one additional case of isolated valvular pulmonic stenosis (case A52-9) was to have been included in this group on the basis of the gross appearance of the valve, but was excluded because the microscopic examination showed only diffuse fibrosis. The remainder of the cases in Table VI appear to be quite ordinary examples of endomyocardial fibroelastosis except for their association with the other anomalies.

Discussion

Ever since the emergence of endomyocardial fibroelastosis as a distinct clinicopathological entity, it has been recognized as a disease process which varies widely from one case to the next, depending upon its position and

somewhat upon the severity of involvement of the subendocardium.[1,2,14,15] As a result of the study of these cases and of those recently reported by Johnson,[6] it is now apparent that the disease is even more pleomorphic than previously suspected, and is capable of latency for a matter of years. Nevertheless, it is apparent that its very variability can lead to the dangerous assumption that all similar changes can be attributed to this process. It is entirely likely that this has been the case not only in the past, but even in this series, in which several cases were included only because no sub-group existed in which to class them. It was with some misgivings that certain of the valvular cases, especially, were included, and, as mentioned, one was somewhat arbitrarily excluded. The two infundibular cases were approached with scepticism, but proved so typical of endomyocardial fibroelastosis that they are included without reservation.

It is at times difficult to judge whether it is Johnson's belief that in certain cases of his series[6] the hypoplastic chambers and valves were due to endomyocardial fibroelastosis or whether the endomyocardial fibroelastosis was due to the hypoplastic chamber which caused stagnation anoxia, or whether the two were merely coexistant. Our data yields evidence of coexistance, but its rarity suggests that it may well also be coincidental. Additional sections in other cases, of course, might have resulted in the discovery of additional foci. The question of premature closure of the foramen ovale, which he raises, is a ticklish one. Evidence for or against this entity could not be determined in this series, nevertheless it is by its very nature impossible to rule it out in all but the eight cases in which the foramen ovale or an auricular septal defect was patent. Three cases are of special note. These show diffuse endomyocardial fibroelastosis with patent foramen ovale or auricular septal defect and no other cardiovascular anomaly. Two of these involved all chambers and valves, the other, all chambers and the aortic valve. While some of the other cases could be fitted into Johnson's anoxic groups, and the possibility cannot be excluded in most of the others, there seems no conceivable cardiovascular reason for such anoxia in these three cases.

From this study several conclusions are evident:

1) Although endomyocardial fibroelastosis is clinically a protean disease, three major groups may be separated. The first dies either before any cardiac pathology is suspected or after a short typical steadily downhill course. The second repeatedly responds to good medical management over a period of months or years after an initial attack of congestive failure in infancy and a few appear amenable to surgical improvement. The third group carries their fibroelastosis well beyond infancy, and it is only logical to believe that a very few may live for a prolonged period with an entirely normal life. This last conclusion, of course, must be confirmed by pathologists with a wider age group than ours, and an alert eye for the minor forms of this disease, which would then prove entirely incidental findings. Several features of Johnson's study tend to confirm this belief.

2) There is no evidence in this material to exclude the possibility that the fibroelastosis may be secondary to other abnormalities in certain

instances. At least three cases, however, rule out the possibility that all cases of endomyocardial fibroelastosis are due to secondary anoxia as suggested by Johnson.

3) Endomyocardial fibroelastosis is by no means one of the great rarities of medicine. The milder forms have been missed or misinterpreted in the past, when it simply was not sought.

4) Endomyocardial fibroelastosis is often associated with other anomalies. For this reason, and since we have seen no evidence of an inflammatory etiology or of collagen or glycogen storage abnormality, we believe it to be an "idiopathic" congenital anomaly.

5) Endomyocardial fibroelastosis is not infrequently associated with hypoplasias and coarctation. Since some slight anatomical similarity exists, if this association continues to be evident in later series, intensive studies of interrelationships will certainly be indicated. Further microscopic study of congenital anomalies of the cardiovascular system is strongly indicated in any event.

6) Endomyocardial fibroelastosis is primarily an anomaly of the subendocardium, with secondary vascular, and tertiary myocardial changes leading typically to compensatory myocardial hypertrophy and eventual dilatation.

7) Endomyocardial fibroelastosis can be the etiology of valvular stenosis, infundibular stenosis, and perhaps hypoplasia of a chamber. Nevertheless, such cases form but a small proportion of the total of all such malformations as the basic pathology of cardiovascular anomalies is presently understood.

8) The valvular form of endomyocardial fibroelastosis is an ill-defined group. Two major types exist, at least in the pulmonic and aortic valves. That which is more commonly seen with the diffuse mural type shows thickening of the cusps which is characterized by a nodular pattern. Microscopically, the mural fibroelastosis may usually be seen entering the base of the leaflet, beyond which the hyperelastosis is lost in a mass of fibrous tissue often arranged in whorls. The second type is essentially indistinguishable from that seen in so-called idiopathic isolated pulmonic or aortic valvular stenosis. In all probability, it is identical with the latter, and is quite different entity from the other just described. The leaflets are diffusely and smoothly thickened, and more or less adherent at the commissures. On microscopic examination, a uniform pattern of simple fibrosis is seen. Intermediate forms exist, but occur generally in the older group and thus appear to represent secondary changes. Whether all cases of incomplete separation of the papillary muscles and other atrioventricular valvular anomalies should be considered a part of the endomyocardial fibroelastotic syndrome is at present a moot question.

SUMMARY

Thirty cases of endomyocardial fibroelastosis are presented. Since this represents a five year period, it is not a rare disease when sought. Over 50 per cent were associated with other congenital anomalies, and possible relationships are suggested. A survival to the age of 20 years is reported,

and major clinicopathological features are discussed. Three cases which do not fit the anoxic concept of Johnson are presented.

RESUMEN

Se presentan 30 casos de fibroelastosis endomiocárdica. Puesto que esto corresponde a un periodo de cinco años, no es un padecimiento raro si se busca. Más del 50 por ciento se asociaron con otras anomalías congénitas y se sugieren las posibles inter-relaciones. Una sobrevida hasta la edad de 20 años se refieren las características clínico-patológicas más destacadas se discuten. Se relatan tres casos para los que el concepto anóxico de Johnson no es adecuado.

RESUME

L'auteur rapporte trente cas de fibro-élastose endomyocardique. Comme cet ensemble se répartit sur une période de cinq années, on ne peut considérer cette affection comme rare quand on sait la rechercher. Plus de 50% des cas se trouvaient associés à d'autres anomalies congénitales et l'auteur étudie leur relation possible. Il rapporte une observation avec survie jusqu'à l'âge de 20 ans, et il met en discussion les principaux éléments cliniques et anatomo-pathologiques. Il présente trois cas qui ne s'accordent pas avec la conception anoxique de Johnson.

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The Continuous and Concurrent Use of Streptomycin, Para-Aminosalicylic Acid, Isoniazid Plus Early Surgery in the Treatment of Tuberculosis

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The development of resistant strains of tubercle organisms is the main problem in using continuous antimicrobial therapy in the treatment of tuberculosis. Streptomycin and isonicotinic acid hydrazide have both been found to have a bactericidal action on tubercle organisms in the laboratory; the action of streptomycin varies directly with the concentration of the drug while the action of the isoniazid appears to be independent of drug concentration. When these two drugs are used together the survival time of both intracellular and extracellular tubercle bacilli is further decreased, as shown by Mackaness and Smith.[1] When used clinically by Pitts, Tempel, Miller, Sands, Fitzpatrick and Weiser[2] the beneficial effects are seen but by the end of four months definite bacterial resistance had developed in five of the 11 patients that were still positive. D'Esopo[3] and others in large government hospitals had established the use of continuous streptomycin and para-aminosalicylic acid. On June 1, 1952, we began our present regimen of administering streptomycin, para-aminosalicylic acid and isoniazid concurrently and continuously from admission to discharge to all patients with pulmonary or extrapulmonary tuberculosis.

Material and Methods

During the year beginning June 1, 1952, 101 cases of proved tuberculosis were admitted to our hospital. Of these 101 treated with the three drugs, nine had been hospitalized elsewhere but none had received previous antituberculosis therapy. All had positive cultures or a diagnosis substantiated by pathological sections. The following table shows background material regarding these patients.

Discharged Patients	60	Male	62
Still Hospitalized	36	Female	39
Deaths	5	White	76
TOTAL	101	Non White	25
Age range from 0-10 years	14	Extent of Disease	
10-20 "	8	Minimal Tuberculosis	4
20-30 "	15	Moderately Advanced	38
30-40 "	19	Far Advanced	38
40-50 "	18	Extrapulmonary	9
50-60 "	9	Primary	12
60 and over	18		

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The adults received 1 gram of streptomycin sulfate intramuscularly twice a week, children under 12 years of age received ½ gram intramuscularly twice a week. Isonicotinic acid hydrazide was administered to all age groups on the basis of 4 mg. per kilo of body weight adjusted to the nearest 50 mg. tablet, and also adjusted as the patient gained in weight. Ten grams of sodium para-aminosalicylate in solution was given daily to adults, and for children the dosage was scaled down according to their weight. No form of collapse therapy was used on this group of patients and they were encouraged to use full lavatory privileges as soon as they were physically able to be up. At the end of three months most of the patients went into the dining room to eat.

Upon admission to the hospital all patients whose sputum was not positive on smear had their gastric contents cultured on three successive days, using modified Lowensteins and Petragnani's media. Gastric contents are cultured monthly until discharge. The original culture is kept for comparison with subsequent cultures to determine whether bacterial resistance to streptomycin or isoniazid is present or if it develops. Roentgenograms of the chest were obtained on admission and at three month intervals. Even old long-standing disease showed some clearing. It is our opinion that the disease remaining after six months represents the destroyed tissue or the scarring resulting from healing. All patients who have not converted their cultures by the end of the third month in the hospital are considered as surgical candidates. Antero-posterior tomographs are taken and bronchoscopy is done.

We recommend surgery when (1) the patient has been positive for three months or more after receiving all three of the antibiotics, (2) when there are extensive localized areas of destruction with or without bronchial stenosis, (3) when the patient is not likely to accept any prolonged period of hospitalization (alcoholics, etc.) and (4) when portions of the lung bound down by adhesions may be salvaged by decortication. If bronchoscopy reveals redness and swelling, then surgery is delayed two to three months and the patient is bronchoscoped again. This bronchitis has constituted a delaying factor for three of our patients. In this series of 22 patients, 25 bronchoscopies have been done.

Twenty thoracotomies with resection have been performed. After surgery, the pathological specimens were cultured using sections of obvious disease, usually from the cavity wall. The following table contains summaries of surgery.

Pulmonary Surgery	Culture Before Surgery	Culture of Specimen
1 Pneumonectomy	Negative	Negative
5 Lobectomies	Negative	Negative
1 Lobectomy	Negative	Positive
1 Lobectomy	Positive	Positive
5 Segmental Resections	Negative	Negative
3 Segmental Resections	Positive	Positive
2 Wedge plus decortication	Negative	Negative

Extrapulmonary Surgery

5 Genito-urinary tuberculosis
- 3 Nephrectomies.
- 1 Bilateral resection of the epididymis plus right orchiectomy; patient has moderately advanced pulmonary tuberculosis.
- 1 Ureteral transplant to the large bowel; 1 kidney functionless, marked involvement of the bladder with stenosis of the ureter where it enters the bladder; also has moderately advanced pulmonary tuberculosis.

5 with Bone Involvement
- 2 Tuberculosis of the knee which have been fused.
- 1 Tuberculosis of the fibula with a sinus tract that was saucerized and the tract excised; also has moderately advanced pulmonary tuberculosis.
- 2 Fusions of the spine, one with pulmonary tuberculosis, the other with a sinus tract from lumbar 5 and the sacrum.

Early surgery is possible because shown roentgenologically, maximum clearing had taken place at the end of six months, with most of the change occurring during the first three month period; and, the acute bronchitis had subsided within three or four months from time of admission so that the bronchus would heal when resected. All of these patients have become negative for tubercle bacilli following surgery and there has been no surgical death, no spread or reactivation of disease on the opposite side, and only one bronchopleural fistula which was closed with primary suture and a small thoracoplasty.

Bacteriological Evaluation:

General improvement in the condition of our patients is comparable to that described by Pitts, et al, when they used streptomycin and isoniazid, and our conversion of cultures is shown in the following table.

Time in Months	1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.	Over 6 mo.
Number Converting	53	21	8	5	5	2	2
Percentage of Conversions	55.2	21.9	8.3	5.2	5.2	2.1	2.1

One patient was streptomycin resistant at onset of treatment and required five months to convert. Six had isoniazid resistant bacilli at the onset of treatment and for five the period of time before conversion was prolonged; two converted at four months, and three at five months. Both who have been positive over six months have developed organisms that are resistant to isoniazid. Both have been resected and are now negative.

Toxic Reaction to the Drugs:

Streptomycin Toxicity: Two dermatitis medicamentosa with elevated temperature and eosinophilia occurred on the 28th day of treatment. After the acute reaction subsided, they were given dihydrostreptomycin and the dosage was continued for four and six months until their discharge without any further difficulty. Two with renal tuberculosis developed toxic nephritis with elevation of blood urea nitrogen which returned to normal level within two weeks after stopping streptomycin.

Para-aminosalicylic Acid Toxicity: Chills, fever and marked prostration occurred in four who had been receiving the drug from 24 to 49 days and any further attempt to administer it resulted in recurrence of the same symptoms.

Isoniazid Toxicity: Only one has had unfavorable reaction to isoniazid. She was a known epileptic who had a recurrence of convulsions but by increasing anti-convulsant drugs it was possible to continue administering isoniazid.

The following table is a summary of the 36 patients still hospitalized and the 60 discharged with regard to extent of disease, average number of months positive, and the amount of therapy that the discharged group received:

	THIRTY-SIX PATIENTS REMAINING IN HOSPITAL		SIXTY DISCHARGED PATIENTS		
Stage	No. of Patients	Average Rate of Conversion	No. of Patients	Average No. Hospital Days	Average No. Months Positive
Minimal	2	1 month	2	243.5	1.67
Moderately Advanced	10	1.7 months	27	200.2	1.67
Far Advanced	17	2.88 months	20	248.3	2.7
Primary	5		4	172.1	
Extrapulmonary (Three with Pulmonary)	5		10	152.3	
			Final Averages	207	2.05

DRUGS RECEIVED	Average No. Days Received	Per cent of Time in Hospital
Streptomycin	194.2	95
P.A.S.	160.9	77
Isoniazids	185.3	90

The periods of time required to convert patients admitted with minimal, moderately advanced and far advanced tuberculosis are surprisingly similar, both in the discharged group of 60 and the 36 remaining in the hospital. The length of their hospital stay is generally about the same regardless of the extent of their disease.

Discussion

When we compare our results using streptomycin, para-aminosalicylic acid and isoniazid with the results of Pitts, et al, using streptomycin and isoniazid, there is little difference between the two programs during the first four months of therapy. Beyond that time, however, the combination of all three drugs seems to be of greater therapeutic value with a higher conversion rate and the emergence of fewer resistant strains of organisms.

The question is raised: Why do not all patients convert their gastric cultures by the end of three months? Bacterial resistance or the development of bacterial resistance accounts for eight of the 14 who did not

convert during the first three months. Three had acute bronchitis and became negative when the bronchitis subsided. Two had poor blood supply to the tuberculous area due to silicosis. The last of the 14, had marked continuous blood loss due to a fibroid uterus and she became negative following hysterectomy when it was possible to maintain her hemoglobin at normal level.

We have not seen intermittantly positive patients. Once they became negative, they remained so even though they were permitted additional activity in the hospital.

There has been great disagreement between the bacteriologist and the clinician regarding the negative cultures found on pathological specimens.[4,5] Since the results of culture from our pathological specimens have been similar to the reports of other authors, and since physical exertion has always been considered the cause of reactivation, we have been returning our patients to their previous occupations and activity immediately upon discharge from the hospital. Many have gone back to hard physical labor, doing farm work, foundry work and carpentry. We examine these every three months and some of this group have been out of the hospital for six months or more. All of these patients have maintained their discharge weights and have no symptoms. There has been no evidence of roentgenological change. These patients have had no chemotherapy since leaving the hospital. We do not know how long the three drug combination should be given, but our patients have received an average of 194 days of streptomycin, 161 days of para-aminosalicylic acid and 185 days of isoniazid out of an average of 207 days in the hospital. If after one year there are no readmissions it would seem that this dosage is adequate.

SUMMARY

1) When we compare the streptomycin-isoniazid combination with our usage of streptomycin, para-aminosalicylic acid and isoniazid, the three drugs used concurrently and continuously have a greater therapeutic value with a higher conversion rate and the emergence of fewer resistant strains of organisms.

2) It is possible to maintain this regimen of therapy on a high percentage of patients because of the few toxic reactions. The cost is negligible.

3) Surgery after four to six months of this three drug regimen is not only safe but it is desirable because it prevents the development of resistant organisms.

4) Sixty patients have been discharged and returned to their previous occupations, regardless of the amount of activity these occupations require. They have shown no roentgenological change, have maintained their discharge weights or gained, and some have already had negative gastric cultures as out-patients.

RESUMEN

1) Cuando comparamos la combinación de estreptomicina-isoniacida con el uso de estreptomicina-PAS-isoniacida, se observa que el uso de las tres

drogas simultáneamente tiene un valor terapéutico mayor con una proporción más elevada de conversiones de esputos y menor emergencia de cepas resistentes.

2) Es posible mantener este régimen de tratamiento en un elevado porcentaje de enfermos a causa de las pocas reacciones tóxicas a que da lugar. El costo no es de consideración.

3) La cirugía después de cuatro a seis meses de este régimen de tres drogas, no sólo es segura, sino que es deseable porque previene el desarrollo de gérmenes resistentes.

4) Se han dado de alta sesenta enfermos que han regresado a sus ocupaciones previas sin tener en cuenta el grado de actividad que tales ocupaciones requieren. No han mostrado cambios radiológicos, han mantenido su peso al salir o han aumentado y algunos, han llegado a tener cultivos gástricos negativos en pacientes externos.

RESUME

1) En comparant l'utilisation d'une part de la streptomycine associée à l'isoniazide et d'autre part de la streptomycine associée au P.A.S. et à l'isoniazide, les auteurs constatent que ces trois produits, administrés simultanément et d'une façon continue, ont une plus grande valeur thérapeutique, négativent plus vite l'expectoration, et provoquent une plus faible résistance des germes.

2) La discrétion des réactions toxiques permet de poursuivre longtemps ce mode de traitement pour une proportion élevée de malades. Le prix de revient en est négligeable.

3) Après quatre à six mois de ce traitement médicamenteux, l'intervention chirurgicale à non seulement perdu ses risques mais en outre elle souhaitable pour éviter le développement de bacilles résistants.

4) Soixante malades ont été autorisés à quitter l'hôpital et à retourner à leurs occupations antérieures, quel que soit le degré d'activité qu'elles exigeaient. Il n'a été constaté chez eux aucune évolution radiologique, ils se sont maintenus au poids qu'ils avaient à leur sortie ou l'ont augmenté, et certains d'entre eux suivis à la consultation ont jusqu'à présent des cultures de tubages gastriques négatives.

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The Clinical Use of Intravenous Sodium Para-Aminosalicylate and Polyvinyl Pyrrolidone*

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Introduction

In a previous report[8] the authors confirmed the work of French investigators[2,3,6] showing that a combination of 25 per cent Sodium Para-aminosalicylate (PAS) in 3.5 per cent aqueous polyvinyl pyrrolidone (PVP) given by intravenous syringe injection results in blood PAS levels which are approximately twice as high and last twice as long in a therapeutic range as does similar injection of 25 per cent PAS without PVP. It was also demonstrated that PVP does not interfere with the antibacterial property of PAS *in vitro* and it does not prevent PAS from passing into the cerebrospinal fluid in adequate amounts. PAS-PVP solution was used therapeutically in a small series of patients for short periods of time without significant toxicity. Therefore it is feasible to use such a preparation in the treatment of tuberculosis and it has an advantage over the usual forms of parenteral PAS in that it may be given in small amounts by syringe injection twice a day.

The purpose of this report is to present further observations on the use of intravenous PAS-PVP in a larger series of patients, including postmortem findings in four. It will also be shown that PAS-PVP has no particular value when given by mouth from the standpoint of the blood PAS levels achieved.

Method

PAS-PVP is provided as a sterile light amber aqueous solution in 10 cc. ampules containing 25 per cent Sodium PAS and 3.5 per cent PVP. For control studies, a sterile aqueous solution of 25 per cent Sodium PAS was used. PAS-PVP was injected intravenously by syringe in 10 cc. amounts twice a day for the purpose of therapy. The injection was made slowly over a period of five minutes. Proportionately smaller amounts were used in children on the basis of body weight.

Blood level curves were determined after the ingestion of 10 cc. of drug solution diluted to 60 cc. with water and followed by 60 cc. of orange juice. Three patients were given PAS-PVP and three were given PAS alone. Specimens of blood were drawn one, three, six and nine hours after administration of the drug and were stored in the refrigerator over night. The following day the PAS levels were determined by the method of Klyne and Newhouse.[5] The resulting curves were compared with the curves ob-

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tained after intravenous injections of the same materials in six patients who were used as their own controls.[8]

Results of Blood Level Determinations

Figure 1 shows that PAS-PVP when given intravenously (A) resulted in much higher and more prolonged PAS blood levels (average values) than does PAS alone given intravenously (B). This figure further shows that the oral administration of PAS-PVP resulted in blood levels (D) which were not significantly different from those obtained after the use of an equivalent amount of oral PAS alone (C) and both of these curves differ only slightly from the curve obtained after intravenous injection of PAS alone. Since PVP is a polymer which is not absorbed from the gastro-intestinal tract, these findings are understandable. It is apparent that PAS-PVP results in elevated and prolonged PAS blood concentrations only when this combination is administered intravenously.

Toxicity of Intravenous PAS-PVP

Table I summarizes the data on toxic reactions in 39 patients treated with intravenous PAS-PVP for periods varying up to four weeks. Twenty-three received treatment for less than one week. Ten died of their disease. It was necessary to discontinue medication in one case because of pain in the region of the biceps muscle above the site of injection during administration of the drug. Other toxic manifestations were insignificant, including transient slight dizziness in a few patients. Treatment was stopped in the rest of these 23 cases when parenteral PAS was no longer necessary.

Ten were treated for one to two weeks and one died of his disease. Therapy was discontinued in one because of thrombophlebitis. Treatment was stopped in the remainder when intravenous PAS was no longer indicated.

Six were treated for two to four weeks and one died of his disease. Thrombophlebitis necessitated discontinuation of therapy in two cases and

TABLE I: TOXICITY OF INTRAVENOUS PAS-PVP IN 39 PATIENTS CORRELATED WITH DURATION OF THERAPY

Duration of Therapy	No. of Patients Treated	TOXICITY — Manifestation	TOXICITY — No. of Patients
Less than 1 week	23	Pain in biceps*	1
		Transient lightheadedness	1
		Phlebothrombosis	1
		Transient nausea and warmth	1
1 to 2 weeks	10	Thrombophlebitis*	1
		Phlebothrombosis	1
2 to 4 weeks	6	Thrombophlebitis*	2
		Phlebothrombosis	1

* Necessitated discontinuation of therapy.

injections were stopped in the other three patients when intravenous PAS was no longer needed.

The indications for intravenous PAS-PVP were as follows: critical forms of tuberculosis such as miliary and meningeal disease, inability to take adequate amounts of PAS by mouth, and major chest surgery for tuberculosis. Those who fell into the latter category were routinely given intravenous PAS-PVP twice a day for one or two days prior to the operation and three or four days after the operation. Because of the possibility that PAS might interfere with the clotting mechanism by lowering the prothrombin level, nine were treated and followed with frequent blood prothrombin determinations; no significant changes were noted.[4]

Four who died were autopsied. They had received two to seven days of treatment before death. No significant histologic change that could be attributed to PVP was found in the various organs. The renal tissue was examined by means of routine H & E, fibrin, mucopolysaccharide and trichrome stains. Excessive granularity was noted in the tubular epithelium by Dr. William E. Ehrich. This was most pronounced in a patient who died of lymphocytic choriomeningitis (diagnosed as tuberculous men-

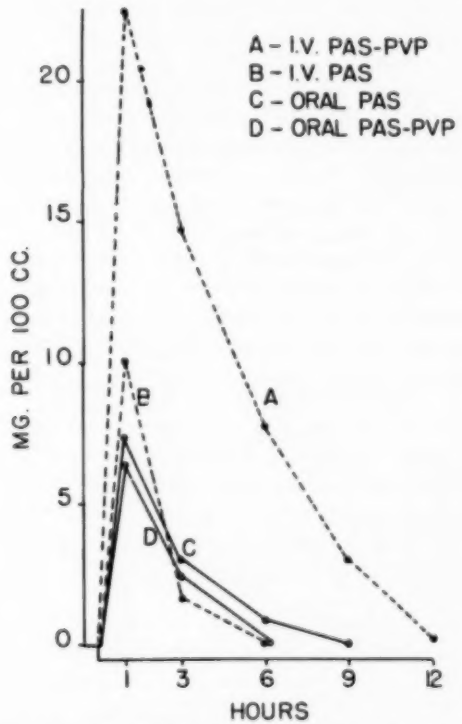

FIGURE 1: Average blood PAS levels after oral and intravenous administration of 2.5 grams of Sodium PAS with PVP and without PVP.

ingitis during life) and constituted what Dr. Ehrich called a "protein storage nephrosis". Whether this was due to the choriomeningitis or to the PVP is difficult to say at this time.

Discussion

Both PAS and PVP[1] have been given intravenously to humans in large amounts without significant toxicity. It is therefore reasonable to assume that the small amounts used in the PAS-PVP solution with the present regimen of therapy for short periods of time are not harmful. The only significant reaction encountered has been local thrombophlebitis in a small percentage of patients after more than one week of treatment. This reaction is undoubtedly due to the high concentration of PAS employed. Since it is uncommon, such reaction does not constitute a deterrant to the use of intravenous PAS-PVP.

PVP is a macromolecular polymer and only 40 to 60 per cent is excreted in the urine during the first few days after infusion. Since no other routes of excretion have been demonstrated, there has been some concern over the ultimate fate of this substance and the possible toxic effects of long term retention. Ravin, Seligman and Fine[7] have studied the excretion, distribution and metabolism of PVP by means of radioactive tracer technics. There is no apparent metabolic degradation of PVP and, since the sole route of excretion is through the kidney, what PVP is not present in the blood is present in the tissues. The highest concentration of PVP is in the organs of the reticulo-endothelial system and retention is longest here. PVP may be excreted in the urine from tissue depots for as long as a year after intravenous infusion. There is, however, no evidence at present that long term retention of PVP is deleterious. Hence it would seem to be safe to use this substance in small amounts for short periods of time in combination with PAS for the treatment of tuberculosis whenever it is advantageous to achieve high blood PAS levels with a minimum of inconvenience and when oral administration of PAS is not feasible. Further discussion of this interesting combination of drugs is contained in our previous report.[8]

SUMMARY AND CONCLUSIONS

A combination of 25 per cent Sodium PAS in aqueous 3.5 per cent PVP solution has been administered intravenously twice a day to 39 patients for various periods of time up to four weeks. The only significant toxic reaction was thrombophlebitis which occurred in three. Postmortem histologic studies in four cases revealed no lesion that could be definitely attributed to PVP. No change in plasma prothrombin level occurred during therapy.

The advantage of this combination lies in the fact that higher and more prolonged blood PAS levels are achieved than can be obtained with equivalent amounts of PAS alone when given intravenously or by mouth. It has been shown that PAS-PVP given by mouth does not result in blood PAS levels which are significantly different from those which result when equivalent amounts of PAS alone are given orally.

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RESUMEN Y CONCLUSIONES

Una combinación de solución acuosa de PAS sódico al 25 por ciento con una solución de PVP se administró intravenosamente dos veces al día a 39 enfermos por various periodos de tiempo hasta cuatro semanas. La única reacción tóxica fué la tromboflebitis que ocurrió en tres. Los estudios post-mortem, histológicos en cuatro casos no revelaron lesiones atribuibles al PVP. No ocurrió cambio en el nivel de protrombina en el plasma durante el tratamiento.

La ventaja de esta combinación radica en el hecho de que se obtienen niveles de PAS más altos y más prolongados que lo obtenido con el PAS sólo cuando se dió por la boca o intravenoso. Se ha demostrado que el PAS-PVP por vía oral no produce niveles de significación diferentes de los que produce el PAS oral solo.

RESUME

L'auteur à administré, par voie intra-veineuse, deux fois par jour, à 39 malades, pendant un temps variable allant jusqu'à quatre semaines, une solution de 25% de P.A.S. sodique dans une solution aqueuse à 3.5% de polyvinyl pyrrolidone. La seule complication de ce traitement fut une thrombophlebite chez trois malades. Dans quatre cas, il fut amené à faire une étude histologique post-mortem, et celle-cine montra aucune lésion qui puisse être sans discussion attribuée au polyvinyl pyrrolidone. Au cours du traitement, il n'y eut aucune altération dans le taux de la prothrombine plasmatique.

L'advantage de cette association thérapeutique réside dans le fait que l'on peut ainsi obtenir des taux sanguins de P.A.S. plus élevés et plus prolongés que ceux que l'on obtient avec des doses égales de P.A.S. lorsqu'il est administré isolément soit par voie intra-veineuse, soit par voie buccale. Il à été démontré que cette association P.A.S.-polyvinyl pyrrolidone, lorsqu'elle est absorbée par la bouche, n'entraine pas d'élévation du taux de P.A.S. sanguin nettement différent de ceux que l'on obtient par l'ingestion buccale de P.A.S. pris isolément.

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The Post-War Tuberculosis Program in the Philippines

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Introduction

The problems faced by the Philippine Commonwealth government at the end of the Second World War included not only those resulting from actual hostilities, but many problems arising from the failure of the Public Health program before the war broke out. In 1941 this program had deteriorated badly and equipment was already obsolete. As a consequence, the danger of large-scale epidemics was great by 1945. The United States came to the assistance of the battered country shortly after the war ended; a budget of $5,000,000 was appropriated for public health rehabilitation. Of this sum, $1,000,000 was specifically set aside for tuberculosis control, since this had long been one of the chief public health problems in the Philippines. The fund was to be administered by the Department of Health of the Philippine Commonwealth and the United States Public Health Service; the Philippine government obligated itself to carry on the program alone at the end of five years.

The tuberculosis control program was worked out by Dr. Leroy K. Young, of the United States Public Health Service, and representatives of various local organizations interested in tuberculosis control. The writer was present representing the director of the Bureau of Health. It was realized by all concerned that the sum allotted was small, in terms of the size of the population (about 20,000,000) of the Philippines, and the seriousness of the tuberculosis hazard. Various approaches were considered, but it was finally decided to adopt Dr. Young's suggestion, and concentrate upon the control program which was proving so successful in the United States at that time—mass chest radiography.

Results of Large-Scale Chest X-ray Survey

In a period of five years, about 1,000,000 people were x-rayed by mobile units or at permanent chest examination stations. Approximately 9 per cent of those examined were found to be suffering from tuberculosis of the lungs. If this rate persists throughout the entire population, it would mean that about 1,800,000 people in the Philippines have active and contagious tuberculosis. Fortunately, there is reason to believe that this rate is not typical of the whole population, but there was confirmation of what was already known, that tuberculosis is a major Philippine health problem.

The survey was otherwise of little consequence, even among those who received x-ray films. For the most part, the active cases of tuberculosis were confirmed and then released. There were no facilities for isolation; we had neither the sanatorium beds nor personnel. The great majority of

these known tuberculous individuals remain untreated, uncared for, unisolated, and free to continue spreading infection. It has even proved impossible to provide medicine and supplementary food for these known cases of clinical disease. This episode became another example of how excellent public health programs can become ineffective and wasteful when they are designed without regard for local conditions.

Further Public Health Measures—BCG

Since we were unable to deal with the cases of tuberculosis that we had, it was obviously foolish to continue to concentrate our program on further case finding, and we were forced to reconsider our approach. The same problem, grossly insufficient funds, remained. At this juncture, BCG was suggested and favorably received. It was felt that since the facilities for isolation, treatment, and education were lacking, immunization was the one remaining approach, offering substantial possibilities. Financial and technical assistance on such a program might be available, it was felt, since the World Health Organization was interested in BCG.

The World Health Organization encouraged this program, and soon after the Philippines became a member, it made available the personnel necessary to begin the undertaking. Dr. Gumersindo Sayago, of Cordoba, Argentina, was among the first workers to arrive; he spent six weeks visiting local chest centers, holding conferences with medical groups, and conducting a two week training course for Philippine medical personnel.

Even before the war BCG had been used in the Philippines, but only on a small scale. Those interested in this early program, including myself, were not particularly impressed with the vaccine at the time, and were inclined to oppose the large-scale program. However, in some degree because of the influence of the World Health Organization, the Philippine government and powerful social groups became enthusiastic. The findings of the early Philippine experiments were neglected in favor of the apparently encouraging reports from South America and Europe. BCG became the official tuberculosis control program of the government and absorbed a great share of the financial resources available. Attempts to reexamine the question have been promptly and firmly discouraged; the writer's protests against the enthusiasm BCG has generated have been bitterly attacked both by officials concerned with the program and by local health leaders.

BCG in the Philippines—Its Feasibility

The writer's interest in BCG is not new; it began about 25 years ago at the Sixth International Conference on Tuberculosis, held in Rome in 1928. Following that conference, and a tour of the leading tuberculosis centers of Europe, the writer summarized his objections to BCG as follows:

"What should be the attitude of Philippine workers toward this vaccine? The controversy which BCG has occasioned would not be so serious if the question raised by its opponents concerned merely the *effectiveness* of the vaccine. But can we really consider the use of this control measure when

acknowledged authorities seriously question its *safety*? Are we justified in subjecting—to borrow the word of von Pirquet—the next generation to the uncertainties surrounding such a vaccination? . . . We must not allow ourselves to be overcome by a well-meaning desire to be pioneers in this new treatment, this biological novelty that promises nothing short of the elimination of the white plague from the whole world."

The writer has been interested in BCG since that time. Literature on the subject has been followed sympathetically; prejudice against a control measure is impossible, if it works. Tuberculosis is our leading health problem in the Philippines and the "number one" killer of our people. If the vaccine could be demonstrated to be as effective as its proponents have claimed, its service in these islands would be incalculable.

However, the status of BCG has not materially improved since 1928. The basic questions raised at the Sixth International Conference are still the basic questions; they have not been answered. In all the publications on the subject since that date there is little that touches upon the fundamental immunizing principle of BCG. There is a tremendous amount of information upon its stability, standardization, optimum dosage, dried versus fresh vaccine, methods and routes of injection, and tuberculin criteria and conversion. The writer searched in vain, however, for new views and fresh research on the great question—the nature of its supposed immunizing properties.

Doubts on this matter can be reduced to six main heads:

(a) What is the nature of the immunological process that is provoked by the entrance of BCG into the human body?
(b) How does BCG respond in standard tests of immunology?
(c) Why is not BCG effective against bovine tuberculosis?
(d) Has BCG even been conclusively proved to be what it is alleged, a strain of attenuated bovine-type bacilli?
(e) Why should it be a hazard in the presence of pre-existing allergy?
(f) What has been clinically established of the effectiveness of BCG?

(a) *The Nature of the Immunological Processes that are Provoked by the Entrance of BCG into the Human Body.* Immunity to a particular disease results from the acquired ability of body tissues to destroy invading germs by intracellular digestion (phagocytosis of Metschnikoff) or by extracellular digestion (phagolysis of Pfeifer). It is a fundamental principle of preventive medicine that such immunization is always specific. Why should tuberculosis be the exception to this principle; why should we inoculate for human tuberculosis with bovine bacilli?

(b) *BCG in the Light of Other Immunological Tests.* It is sufficiently established that the blood serum of animals immunized to a given bacterium develops biological products not found in the serum of non-vaccinated animals. One of these elements is *specific precipitins* (Kraus); when the blood serum of an animal immunized against a given bacterium is mixed with a culture filtrate of emulsion of that same organism, a "precipitate" or protein deposit results. *Specific agglutinins* (Gruber and

Durham) show a similar reaction with the difference that an agglutinate rather than a precipitate is formed. In both instances the reaction is specific; cholera serum precipitates only cholera filtrate, and so on.

The question is: "Have the Calmette-Guerin bacilli and the blood of those vaccinated with it been studied for these reactions?" The answer is silence. The vast literature and the large number of experiments done on BCG pass the question by—significantly, we think.

(c) *The Effectiveness of BCG in Bovine Tuberculosis.* The seriousness of the failure of BCG to meet standard immunological tests is magnified by its peculiar failure to confer immunity where such immunity would most reasonably be anticipated—in the treatment of cattle. Again, literature is apt to be non-contributory so far as concrete evidence is concerned. The most prominent fact is that in the countries, such as the United States, where bovine tuberculosis is under firm control, this has been accomplished *without* vaccination. BCG was given extensive trial but did not seem to be efficacious among cattle. The Joint FAO WHO Panel on Brucellosis on the subject of bovine tuberculosis concluded the following:

"Vaccination of livestock, particularly with BCG, may be considered a temporary expedient, applicable under certain conditions of economic hardship when it is necessary to reduce the spread of the disease before eliminating the infected animals. Vaccination has its disadvantages: it may create an allergy non-distinguishable from natural infection; intravenous injection of BCG—which sometimes replaces subcutaneous injection—may produce local or general reactions. Vaccination must therefore be used with caution."

The plain fact is that in no instance has bovine tuberculosis been controlled by the use of BCG. Surely this compound cannot be taken seriously among scientists until some explanation is advanced to explain this unique finding, that a vaccine is more effective against a related but distinct organism than it is against its own parent strain.

(d) *Is BCG Conclusively Proved to be a Strain of Bovine-Type Bacillus Rendered "Non-Pathogenic"?* In contemplating the scientifically incomprehensible findings that have been advanced for BCG, we have occasionally been assailed by a grave misgiving. Are the organisms in this vaccine really attenuated bovine bacilli at all? Or are they only saprophytes, such as Moeller's Timothy Bacillus? We have been assured that this doubt is fantastic, but if so, this can readily be demonstrated. The "personality" of BCG can easily be established by repeating the experiments of Calmette and Guerin and duplicating their results. In the many years that BCG has been studied, this simple procedure has never been done; all of our BCG serum is derived from the original experiments.

(e) *The Positive Untoward Effect of BCG when Injected into Persons with Naturally-Established Tuberculin Allergy.* By all immunologic criteria, a person who is tuberculin-allergic should be one who has a pre-existing tuberculosis infection and thereby already possesses the blood elements which confer specific resistance to subsequent infection. Physicians are constantly cautioned that BCG should not be administered to such persons.

Why? If BCG consists of non-pathogenic bovine tubercle bacilli, as is claimed, there is no conceivable immunologic theory that could account for untoward effects in this instance. Obviously, untoward effects are to be feared. The only situation in which such effects might be feared is if human tuberculosis were so different from bovine that it could not immunize against the latter, but provided instead a fertile situation for bovine pathogens of a low grade of virulence. It would require, in other words, the assumption that some degree of virulence was present in BCG.

(f) *The Positive Role of BCG in Reducing Clinical Infection.* The proponents of BCG do not spend much time in a defense of the theory underlying the preparation; in this instance, scientific understanding and control are of less interest than clinical evaluation. But even here unscientific methods make published results of dubious value.

The most enthusiastic reports on BCG came from South America. I think most students would admit, however, that the failure to provide adequate control groups makes these experiments of little value as evidence for BCG.

Most weight is given to the widespread use of the vaccine in the Scandanavian countries, France and Japan. In any of these situations, it is foolish to credit BCG with all progress, without evaluating other factors. In Sweden, for instance, the part played by an increased standard of living and education on the falling morbidity rate is perhaps impalpable, but it is certainly large. In France the situation is similar. Anderson, in a paper presented to the National Tuberculosis Association in 1950, commented on BCG in that country as follows:

"In view of the attitude toward BCG, which has been maintained in this country for so many years, it appears that we have something of an obligation to answer our own question and to prove, before it is too late, just what this vaccine could do in our population. We have before us, the example of France, where BCG vaccination was begun nearly thirty years ago, where compulsory legislation was enacted last year, and yet where no reliable data could now be obtained, as to what part BCG has played in the history of tuberculosis in the country as a whole. We cannot give unqualified credence to the assertion, that a general marked decline in tuberculosis morbidity and mortality in France and Denmark or any other country where BCG has been used, constitutes evidence that BCG was effective."

In Japan a campaign of inoculation has been undertaken with the most exaggerated claims advanced as to its effectiveness. Of the conviction advanced there by individuals on the SCAP staff and local public health leaders, that BCG could arrest the increasing incidence of tuberculosis and prevent the appearance of all but a few new clinical cases, Myers wrote, "Such a result has never been approached anywhere by the use of a vaccine." According to Dr. Akira Saita, in a statement made in September, 1951, "Tuberculosis is the major disease in Japan today, and is causing the greatest number of fatalities." He added that deaths due to tuberculosis were about 150,000 yearly, with 10 times that number of active cases.

It is somewhat surprising to find proponents of BCG using the World

Health Organization's vaccination of 50,000,000 children as evidence for BCG's further use. The effect of this mass inoculation has not, and cannot be, evaluated. As evidence for or against BCG, it can be anticipated with confidence that this program will always be meaningless. The diverse training of technicians, the lack of standards for interpretation, most especially the lack of a system of controls, guarantees that the results of this gigantic undertaking will always remain an enigma.

It is our conviction that in none of these instances has the effectiveness of BCG been put beyond dispute. Most of the large-scale applications have been debated for 10 years, and authorities on tuberculosis remain unconvinced. No other tuberculosis control measure has been so questionable after such a long period of use. The opponents of this measure are being asked, for the time being, to stop being men of science; to accept this vaccine without the rigorous demonstrations of its harmlessness and effectiveness that are demanded of other medical preparations.

Conclusions

The writer is quite aware of the fact that this article will be interpreted as another hypercritical attack on BCG. However, personal considerations should not be allowed to influence judgment upon so important a matter. It is our dispassionate conviction that BCG has not proved itself elsewhere, and there is no reason to anticipate that it will have any greater effect in the Philippines than it has had in Japan. It is particularly unfortunate that this remedy should appear hard on the heels of our disappointment with mass surveys. BCG represents a continuation of our effort to deal with tuberculosis without taking into account the local conditions in which the disease is generated.

All students would agree, of course, that the factors which contribute to our high morbidity and mortality rates can be adequately summarized in one word: poverty. On the one hand, there is ignorance of the most elementary sanitary methods, malnutrition and overcrowding; on the other hand, lack of facilities for isolation and treatment of known cases of disease, lack of trained personnel, and even lack of finances for medication.

In this situation, it requires no very great amount of imagination to devise a health program that could be guaranteed, over a period of time, to accomplish our ends. It would involve the following:

(a) Nation-wide education in sanitation and domestic science.
(b) A program of hospital construction simultaneous with case-finding work.
(c) A vigorous government program directed to improvement in the standard of living, including provision for housing and social security measures designed to eliminate malnutrition.

All leaders in public health would agree that these measures are the fundamental ones to tuberculosis control; perhaps all would agree that tuberculosis will remain with us as a serious public health problem, BCG or no, until these measures are undertaken. There is, nevertheless, no concerted drive at the present time for such a program.

The fact is that public health officers are trying to be doctors and legislators at the same time. As men of medicine it would seem that their one duty is to diagnose the problem and prescribe the best treatment; it is up to the Philippine Commonwealth to meet the prescription as best as it is able. The medical profession should be inflexible in its diagnosis; it does not dare encourage the laymen responsible for implementing its program with false confidence in less than the most desirable way of meeting the problem. If money *must* be had for an adequate public health program, a lot more will be available than first appeared possible.

Instead, our medical officers are being "realistic". Their attitude is well summarized by the following:

"As a public health man, I consider tuberculosis in this country a major epidemic, which requires immediate and drastic measures. The tested methods of hospitalization and treatment are beyond our means. Education, another tested weapon, is too slow . . . It seems reasonable, therefore, to try BCG vaccination en masse. It is the cheapest and only measure within our means."

I suggest that it is not "reasonable" to substitute a remedy of doubtful effectiveness, an unknown quantity, for the tried and proved remedy because the latter is "too expensive". No doctor would consider such an approach in dealing with a patient. When a patient suffers from an operable malignancy, the doctor must insist upon the necessity of the operation. To encourage such a patient to have faith in an antibiotic because he could not afford the operation would be deriliction of duty. Yet that is exactly what we do as public health officers.

It is our obligation to describe the methods necessary to the accomplishment of the objective, the elimination of tuberculosis, and then to administer the outlined program to the full extent permitted by the funds made available. We are not legislators, calculating on the basis of what is legislatively desirable. It is generally agreed that a broad program of public health is the surest and, in the long run, the quickest way to achieve our objective. It is our duty to insist upon this fundamental fact without compromise and without allowing the problem to be obscured by unproved short-cuts. Many years ago Professor Vaughan of Ann Arbor said concerning tuberculosis in the Philippines:

"I went through your tenement districts yesterday and I want to say quite emphatically that as long as such districts continue in your city and in your country, you are not likely to get rid of tuberculosis. I went up to a house and I found there was no light except that which came through the doorway. I went to the kitchen, and I saw the conditions under which the food was prepared. I want to say frankly that I do not believe that you can do very much in the eradication of tuberculosis in this country as long as such tenement houses exist."

There is no evidence at this time that BCG fundamentally alters Dr. Vaughan's analysis. Poverty is still the problem. BCG can only waste money, however, little, that might otherwise be used to combat the disease at its root, and it can only encourage laymen in the false conviction that

a short-cut can be found. In view of the knowledge available about BCG, any public health agency which considers making specific recommendations for a mass BCG program assumes a large responsibility.

SUMMARY

1) During a recent five year period, 1,000,000 persons in the Philippines were examined and approximately 9 per cent were found to be suffering from tuberculosis. While this is probably a higher percentage than exists throughout the Islands, it is a reasonably good criterion of the magnitude of our problem.

2) When these cases were found, facilities were not available for isolation or adequate treatment so they remained free to continue spreading infection. It was not even possible to provide medicine and supplementary food for them.

3) BCG had previously been used in the Philippines on a small scale but without impressive results. However, it was suggested and strongly encouraged by the World Health Organization as the method of solving the problem.

4) BCG has become the official tuberculosis control program and has absorbed a great share of the financial resources available to combat tuberculosis.

5) Nowhere has the effectiveness of BCG been placed beyond dispute. Authorities on tuberculosis remain unconvinced of its value. Opponents of BCG are asked for the time being to stop being men of science but to accept this vaccine without the rigorous demonstration of its harmlessness and effectiveness that are demanded of other medical preparations.

6) BCG has not proved itself elsewhere and there is no reason to anticipate that it will do so in the Philippines. It can only waste money that might otherwise be used to combat the disease at its roots and it can only encourage laymen in the false conviction that a short-cut can be found.

7) The only program that offers any promise of controlling tuberculosis in the Philippines consists of nation-wide education, sanitation, hospital construction for isolation simultaneous with case finding and a vigorous government program directed to improvement of the standards of living. Until these measures are undertaken, tuberculosis will remain with us as a serious public health problem, BCG or no. It is our duty to insist upon the fundamental program so successfully employed elsewhere and to avoid unproved short-cuts.

RESUMEN

1) Durante el último período reciente de cinco años se examinaron 1,000,000 de personas en las Filipinas y aproximadamente se encontró que 9 por ciento sufrían tuberculosis. Si bien este es un porcentaje más alto que el que existe en todas las Islas, es un criterio razonable para estimar la magnitud del problema.

2) Cuando se encontraron estos casos, no había facilidades para el aislamiento o el tratamiento adecuado, de manera que continuaron disemi-

nando la infección. Aun el proveerlos de medicinas y alimentación suplementaria no fué posible.

3) El BCG, se había usado previamente en pequeña escala, pero sin resultados impresionantes. Sin embargo, su empleo fué sugerido y fué alentado por la organización Mundial de la Salud, como el método adecuado para resolver el problema.

4) El BCG, ha venido a ser el método oficial para dominar la tuberculosis y ha absorbido una gran parte de los recursos financieros existentes para combatir la tuberculosis.

5) En ninguna parte se ha demonstrado la efectividad del BCG. Las autoridades en tuberculosis permanecen no convencidas de su valor. A los opositores del BCG, se les ha pedido que por el momento dejen de ser hombres de ciencia y que acepten esta vacuna sin la rigurosa demostración de inocuidad y efectividad que se piden a otras preparaciones médicas.

6) El BCG, no ha dado pruebas de eficacia en otras partes y no hay razón para prever que así resulte en las Filipinas. Sólo puede consumir el dinero que podría emplearse de otra manera para erradicar la enfermedad y puede sólo alentar alas personas fuera de la profesión en la convicción falsa de que puede encontrarse un camino más directo.

7) El único plan que ofrece alguna promesa de dominar la tuberculosis en las Filipinas, consiste en la educación amplia, la mejoría sanitaria, la construcción de hospitales para el aislamiento simultáneo con el descubrimiento de los casos y un plan de gobierno tendente a la mejoría del nivel de la vida.

Hasta que estas medidas se pongan en práctica, la tuberculosis permanecerá entre nosotros como un serio problema de la salubridad, ya se use el BCG o no. Es nuestro deber insistir sobre el plan fundamental tan satisfactoriamente empleado en otras partes y evitar no demostrados caminos breves hacia la meta.

RESUME

1) Pendant ces cinq dernières années, 1,000,000 d'individus ont été examinés aux Philippines et on dénombra parmi eux environ 9% de tuberculeux. Bien que ce pourcentage soit probablement plus élevé que celui de l'ensemble des îles, il représente legiquement un bon critère de l'ampliitude du problème.

2) Après l'identification de ces cas, il n'a pas été possible de leur donner les facilités d'isolement ou de traitement et ils persistèrent à semer la contagion. Il n'a même pas été possible de leur accorder des médications et un supplément de nourriture.

3) Le B.C.G. a été utilisé précédemment aux Philippines sur une petite échelle, mais sans résultats impressionnants. Toutefois, il a été conseillé et fortement encouragé par l'Organisation Mondiale de la Santé comme le procédé susceptible de résoudre la question.

4) La vaccination par le B.C.G. est devenue le programme officiel de la lutte contre la tuberculose et a absorbé una grande part des ressources attribuées à cette lutte.

5) Nulle part le B.C.G. n'a été considéré comme ayant une efficacité indiscutable. Des personnes qui font autorité en phtisiologie n'ont pas été convaincues de sa valeur. On demande à ceux qui s'opposent à la pratique du B.C.G. de cesser pour l'instant d'être des hommes de science et d'accepter ce vaccin sans avoir la démonstration d'innocuité et d'efficacité que l'on demande aux autres produits.

6) Le B.C.G. n'a fait, en aucun autre lieu, le preuve de son efficacité et il n'y à aucune raisen d'imaginer qu'il en sera autrement aux Philippines. Il ne servira qu'à gâcher les ressources pécuniaires qui auraient pu d'une autre façon être utilisées à s'attaquer aux racines du mal. Il ne servira qu'à répandre la fausse conviction qu'il est capable de simplifier la lutte contre la tuberculose.

7) Le seul programme qui offre quelque espoir de vaincre la tuberculose aux Philippines consiste en une éducation sanitaire étendue, en la construction d'hôpitaux permettant l'isolement des malades à mesure qu'on les dépiste et en une action gouvernementale énergique pour l'amélioration du standard de vie. Tant que ces mesures n'aurent pas été mises en route, la tuberculose restera un grave problème de santé publique, qu'on utilise le B.C.G. ou qu'on ne l'utilise pas. L'auteur considère que son devoir est d'insister sur le programme fondamental qu'il estime avoir été la cause des succès obtenus dans les autres pays et d'àviter l'utilisation de procédés dont l'efficacité n'a pas été démontrée.

Multiple Puncture and Intradermal BCG Vaccination

A Quantitative Comparison in Terms of Allergy Production

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In the many mass BCG vaccination campaigns conducted by the International Tuberculosis Campaign during 1948-51,[1] only the intradermal (I.D.) method was used; extensive experience was accumulated about the practicability of the method and level of post-vaccination allergy produced. However, when the Philippine Department of Health, with the assistance of WHO and UNICEF, started a nation-wide BCG vaccination campaign in October 1952, the multiple puncture (M.P.) method was selected for various reasons as the method of choice.

It was S. R. Rosenthal[2] who, in 1939, described and developed the M.P. method of giving BCG vaccine and reported that satisfactory post-vaccination tuberculin allergy could be obtained with this technique. A good many other investigators have subsequently used this method and reported varying conversion rates. One quantitative study of the allergy resulting from multiple puncture vaccination was performed by the United States Public Health Service,[3] but no direct quantitative comparison of the multiple puncture and intradermal methods of vaccination, in terms of post-vaccination tuberculin allergy, was found in the available literature.

The present study was therefore designed to measure and compare the level of post-vaccination allergy obtained by giving the same batch of vaccine intradermally and by multiple puncture to comparable groups of school children.

Material and Methods

The pupils in the three largest public elementary schools in Manaoag Municipality comprised the study. Manaoag is situated in Pangasinan Province, a densely populated, tropical lowland of rural character in the central part of Luzon, the main island of the Philippines.

The three schools had a total enrollment of 3,034 pupils. Those present on the days of pre-vaccination testing, October 7 to 9, 1952—altogether 2,632 children (1,213 boys and 1,419 girls, aged 5 to 17 years), were given a tuberculin test with 5 TU (0.0001 mg. in 0.1 ml.) injected intradermally. The tuberculin dilution was prepared in the Philippine BCG Laboratory from a stock solution of PPD (RT XXII) sent from the State Serum Institute in Copenhagen, Denmark. (The same dilution was used for all pupils given pre-vaccination tuberculin tests in this study.)

All reactions were read at 72 hours. The site of the test was carefully palpated and the transverse diameter of the perceptible induration measured with a millimeter ruler. Only persons with indurations of less than 6 mm. in diameter were considered eligible for vaccination.

The vaccine was given alternately by the intradermal and by the multiple

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puncture method as the children came down the line to be vaccinated. This rotation system was used to eliminate bias in the allocation of non-reactors to the two vaccination techniques. Hence, the results could be compared with a reasonable degree of assurance that differences in post-vaccination allergy, if any, would be due to the vaccination technique and not to systematic differences between the two groups of children.

The BCG vaccine used in the study was produced by the Philippine BCG Laboratory in Alabang. The vaccine for intradermal injection was prepared to contain 1 mg. BCG/ml. and for multiple puncture 20 mg./ml. Both vaccines were prepared from the same harvest of BCG (Batch No. 102) and stored under the same conditions until the moment of vaccination. The vaccines were used within two weeks after harvest.

The techniques of vaccination were as follows:

a) *Intradermal Method:* 0.1 ml. of vaccine was injected as superficially as possible into the skin of the left deltoid region. The skin was not cleansed before the injection.

b) *Multiple Puncture Method:* A modified Rosenthal method was used. The skin was not cleansed before vaccination. One drop of the vaccine was pipetted onto the skin of the left deltoid region. The drop was smeared out over an area of about 2 by 4 cm. The skin on this area was then perforated (40 punctures in four rows of 10 each) with a straight surgical sewing needle. For each puncture the needle was held tangentially to the skin and its point inserted into the skin. An upward movement was then made without withdrawing the needle to ensure that the needle penetrated the upper layer of the skin.

The personnel in the team consisted of Dr. Artenio Serquina and Mrs. Rosa R. Ocximer from the Philippine National Chest Center, Manila, and the writer. Dr. Serquina and Mrs. Ocximer performed all the pre- and post-vaccination tuberculin testing, and the writer read all the reactions. Dr. Serquina gave the intradermal and Mrs. Ocximer the multiple puncture vaccinations.

The type of vaccination and the giving and reading of tuberculin tests were recorded on an individual record card for each child. For purposes of identification each card also gave the name, age and sex of the child as well as name of school, teacher and grade.

Sixteen weeks after vaccination (January 26 to 30, 1953) the team returned to the three schools to give intradermal 5 TU tuberculin tests to the vaccinated children. The tuberculin dilution was prepared by the laboratory in Alabang from the same lot of stock solution that had been used for the pre-vaccination tuberculin testing. The reactions were again read at 72 hours, and the work was arranged so that the reader, when reading the tuberculin reactions, could not know what method of vaccination had been used for each child. This was done in order to exclude any bias deriving from the reader's expecting or hoping for a certain difference in the size of post-vaccination reactions between the two groups.

The total number of pupils tested, vaccinated and retested is given in the following table by school and method of vaccination:

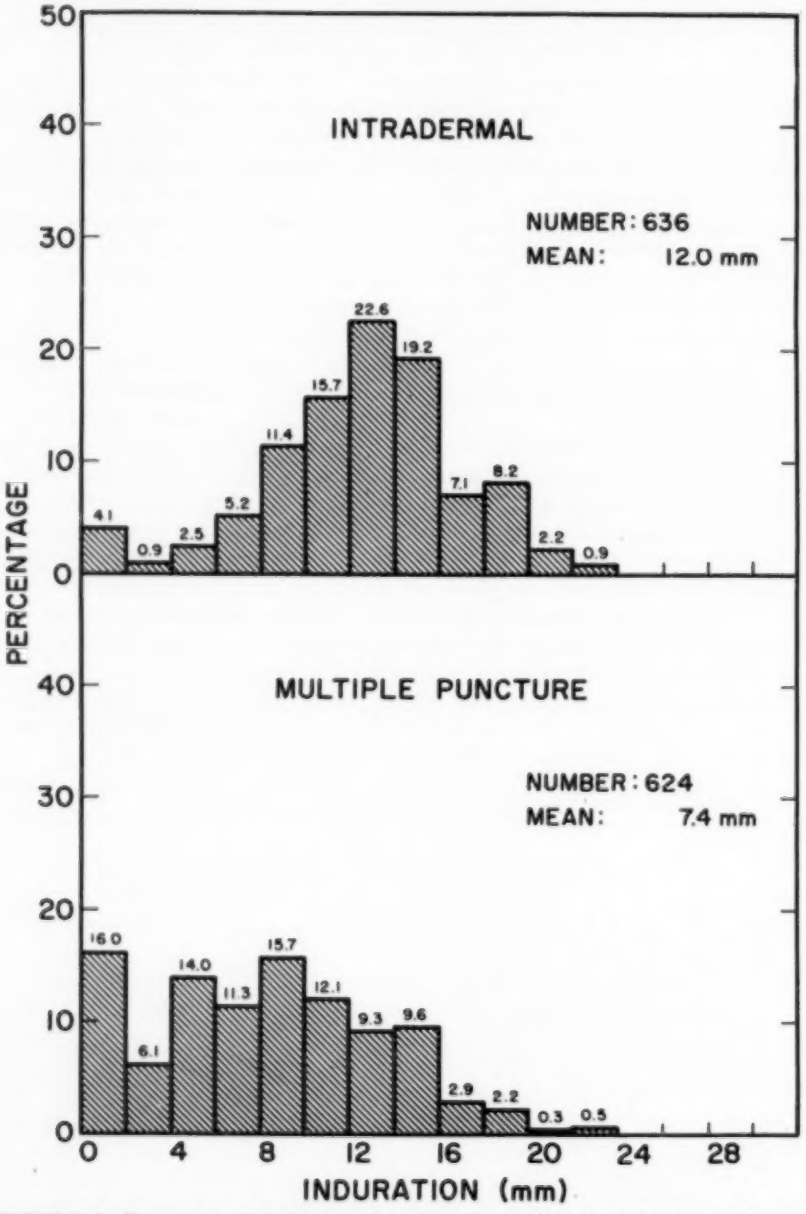

FIGURE 1: Frequency distributions by size of reactions to intradermal 5 TU tuberculin tests in school children 16 weeks after vaccination intradermally (upper section), or by multiple puncture (lower section). —Manaoag Municipality, Pangasinan Province, Philippines, January 1953.

Name of School	Enrollment	Pre-vacc. Test	Vaccinated		Post-vacc. Test	
			I.D.	M.P.	I.D.	M.P.
Manaoag Cent. School	1703	1548	486	484	387	383
Laoac Elem. School	734	612	229	227	141	137
Cabanban Elem School	597	472	160	168	108	104
TOTAL	3034	2632	875	879	636	624

The figures for the pre- and post-vaccination testing include only the children who completed the test, i.e. who returned for the reading of the test.

Results

Post-vaccination Tuberculin Allergy:

The level of tuberculin allergy in each of the two groups appears from the frequency histograms in Figure 1 giving the distribution by size of induration to Mantoux 5 TU of the 636 children vaccinated by the intradermal and the 624 vaccinated by the multiple puncture method.

For the group vaccinated intradermally, reactions measuring 12 to 13 mm. are most frequent, and nearly 60 per cent of all reactions are between 10 and 16 mm. in diameter. For the group vaccinated by the multiple puncture method there is no modal point: the reactions are spread fairly uniformly over a range of 0 to 16 mm. The mean size of reactions is 12.0 mm. for the intradermal group, with about 93 per cent measuring 6 or more mm. in diameter, compared with a mean of 7.4 mm. for the multiple puncture group and only about 64 per cent measuring 6 or more mm. in diameter.

Another difference between the two distributions is the high frequency (16 per cent) of persons with little or no perceptible induration (recorded as "0" or "1" mm.) in the group vaccinated by the multiple puncture method in contrast to only 4.1 per cent in the group vaccinated intradermally.

The frequency of small reactions, those measuring from 0 to a few millimeters, is not correlated with age: the proportion of small reactions is about the same for all ages in the present material.

Pre-vaccination Tuberculin Allergy:

The frequency distribution by diameter of induration of the pre-vaccination 5 TU tuberculin reactions is shown in the upper section of Figure 2. Ordinarily distributions by size of pre-vaccination tuberculin reactions (to 5 or 10 TU) show a concentration of the reactions into two rather distinct groups—one of small and zero reactions (the non-infected) and one of fairly large reactions (the infected). In the present distribution, however, no clear separation is apparent.

A way to interpret the pattern of tuberculin sensitivity shown in the figure is suggested by comparison with a similar pattern found with 5 TU tests in Madanapalle, South India, by teams from the Field Research Station of the WHO Tuberculosis Research Office.[4] The results in India were interpreted on the basis of extensive studies in different countries as indicating the presence of three groups in the population: one group with little

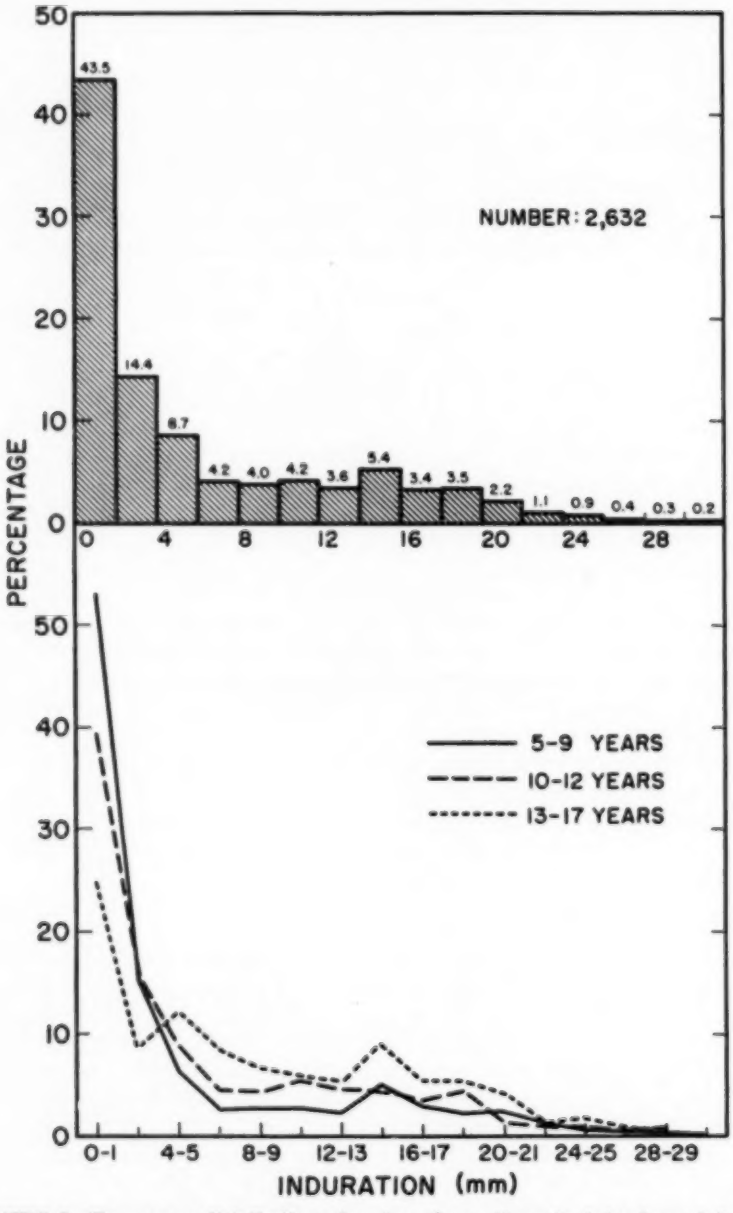

FIGURE 2: Frequency distributions by size of reactions to intradermal 5 TU tuberculin tests in school children, for all ages (upper section), and for three age groups (lower section). —Manaoag Municipality, Pangasinan Province, Philippines, October 1952.

or no reaction, the non-infected; one group with large reactions, the infected; and an intermediate group with a low-grade kind of sensitivity of non-specific origin, i.e. not specific for tuberculous infection. The usual separation of infected from non-infected was thus obscured by interposition of the group with low-grade sensitivity, resulting in a distribution in which the separate segments could not be easily distinguished.

The present findings might be interpreted in the same way. Inspection of Figure 2 reveals at least some concentration of large reactions 14 to 15 mm. in diameter, probably the modal point for the group with the high-grade kind of sensitivity commonly associated with specific tuberculous infection. Separating the study population according to age, as in the lower section of the figure, tends to support this interpretation: the frequency of strong reactions increases with age but there is no apparent change in the form or position of a modal group centering around 14-15 mm.

Assuming, for the moment, that the level of allergy produced by natural infection averages around 14 to 15 mm. to the 5 TU test, one may then have a basis for evaluating the level of allergy produced by BCG vaccination in this study. With the intradermal method, the level of BCG-induced allergy four months after vaccination was nearly as high as that produced by natural infection. With the modified multiple puncture method used, the level was considerably lower.

As the results of the present study clearly showed that a higher degree of tuberculin allergy resulted from intradermal BCG vaccination than from multiple puncture, the intradermal method was used for the mass BCG vaccination campaign in the Philippines.

Discussion

The tuberculin reactions of the children vaccinated by multiple puncture in this study averaged 5 mm. smaller than those vaccinated intradermally. From field investigations of the quantitative effect on post-vaccination allergy of serial dilutions of BCG vaccine,[5] it may be estimated that a difference of 5 mm. in mean reaction size reflects a 10 to 100 fold difference in dose. Thus, the children vaccinated intradermally in the present study may have received, in effect, a dose of BCG at least 10 times larger than the children vaccinated by multiple puncture.

Rosenthal has recently recommended that the strength of the liquid vaccine used for vaccination by the multiple puncture method (30 to 36 punctures) should be raised from 15-20 mg./ml. to 35 mg./ml.[6] As previously mentioned, the strength of vaccine we used was 20 mg./ml. Although our material can furnish little information on the point, it would seem unlikely that our results with multiple puncture would have been appreciably affected had we used the higher dose.

Apart from the matter of dosage, the question of the effect of exposing vaccine to light should also be considered, as it is now recognized that BCG organisms are rapidly killed by light. As vaccination by multiple puncture may involve both a longer and a more intense exposure of vaccine during as well as immediately after vaccination, it is possible that at least part

of the difference in results between the two methods used here might be accounted for in this way. This phenomenon is, however, not likely to have accounted for much of the difference as all vaccinations in the present study were carried out in the shade, never in direct sunlight. In this connection the difference in time of giving an intradermal and a multiple puncture vaccination was negligible (less than one minute), and most of the children covered their shoulders with blouse or shirt sleeves after vaccination.

SUMMARY

The present study was set up in connection with the WHO/UNICEF-assisted BCG vaccination campaign in the Philippines in order to measure and compare the degree of tuberculin sensitivity produced by the intradermal and by a modified multiple puncture method of vaccination.

In Manoag Municipality, 2,632 school children were given an intradermal tuberculin test with 0.0001 mg. of PPD (Mantoux 5 TU) and the 1,754 non-reactors to this test were given BCG vaccine alternately by the intradermal and the multiple puncture methods. Sixteen weeks later the vaccinated children were retested with 5 TU. In reading the reactions, precautions were taken to assure that the reader could not know which method of vaccination had been used in each child.

The tuberculin reactions of children vaccinated intradermally averaged 12.0 mm. in diameter—a level of allergy almost as high as that produced by natural infection: the tuberculin reactions of children vaccinated by multiple puncture averaged only 7.4 mm. in diameter. As a result of this study, intradermal vaccination replaced the multiple puncture method for the mass BCG campaign in the Philippines.

Grateful acknowledgment is made to Dr. Sixto A. Francisco, Chief of the Tuberculosis Division, Philippine Department of Health and members of his staff, whose interest and assistance made the present field work possible; and to the staff of the WHO Tuberculosis Research Office, Copenhagen, for critical comments and help in preparing the paper.

RESUMEN

Este estudio se realizó en conexión con la WHO-UNICEF que ayudó a la vacunación con BCG en Filipinas para medir y comparar el grado de sensibilidad tuberculínica producidas por la vía intradérmica y por un método modificado de la múltiple puntura.

En la municipalidad de Manoag se aplicó a 2,632 niños escolares una dosis de 0.0001 mg. de PPD (Mantoux 5 TU) y a los 1,754 de éstos que resultaron negativos a esa prueba, se les aplicó BCG tanto por la vía intradérmica, como por puntura dérmica en casos alternados.

Dieciseis semanas después, los niños vacunados fueron otra vez sujetos a la prueba con 5 TU. En la lectura de las reacciones se tuvo cuidado para asegurarse de que el observador no pudiese conocer qué método se había usado en cada niño.

Las reacciones tuberculínicas en los niños vacunados intradérmicamente,

dieron una dimensión media de 12 milímetros de diámetro, un nivel de alergia casi tan elevado como el producido por la infección natural; las reacciones tuberculínicas en los niños vacunados por puntura múltiple, sólo daban una media de 7.4 mm. de diámetro.

Como resultado de este estudio, la vacunación intradérmica substituyó a la puntura múltiple en la campaña de vacunación en masa por el BCG en las Filipinas.

RESUME

Ce travail à été établi en relation avec la campagne de B.C.G. organisée aux Philippines par l'O.M.S. et l'UNICEF. Son objet est de mesurer et de comparer le degré des réactions tuberculiniques obtenues par vaccination, en comparant la voie intradermique et une méthode modifiée des piqûres multiples.

Dans la ville de Manoag, 2.632 écoliers furent soumis à une inoculation intra-dermique de tuberculine, dosée à 0.01 milligramme de tuberculine purifiée (ou dosée à cinq unités). Les 1.754 enfants dont les réactions furent négatives, furent vaccinés par le B.C.G., les uns par voie intradermiques, les autres par la méthode des piqûres multiples. Seize semaines plus tard, les enfants qui avaient été vaccinés furent de nouveau soumis à la réaction tuberculinique avec une dose de cinq unités de tuberculine. Pour la lecture des réactions, toutes les précautions avaient été prises afin de s'assurer que ceux qui étaient chargés de les préciser n'avaient pas pu prendre connaissance de la méthode qui avait été utilisée pour chaque enfant.

Les réactions tuberculiniques des enfants vaccinés par voie intra-dermique présentèrent en moyenne un diamètre de 12 millimètres, ce qui implique une allergie environ aussi élevée que celle produite par l'infection naturelle. Des réactions tuberculiniques des enfants vaccinés par la méthode des piqûres multiples ne donnèrent en moyenne que des réactions de 7 mm., 4 de diamètre. A la suite de cette étude, pour la vaccination collective par le B.C.G. dans les Philippines, on à remplacé la méthode des piqûres multiples par la vaccination intra-dermique.

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Serial Chest Roentgenograms: An Evaluation*

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Many pulmonary diseases have long periods of latency and therefore go unrecognized until symptoms become manifest. Failure to apply techniques for early recognition of such abnormalities may result in unduly long periods of treatment, chronic invalidism, or hopeless prognosis.

The simplest way of detecting most early pulmonary disease is by roentgenographic study of the chest. This method of case-finding is more effective if these studies are repeated at intervals. The availability of previous roentgenograms for comparison enhances the reliability of interpretations and illuminates the whole controversial matter of the accuracy of readings based on single films.[1]

Serial chest x-ray films have been available on Philadelphia foodhandlers since January 13, 1947, when the City provided a photofluorographic unit for the annual chest x-ray films which had just been made mandatory for this group of workers. About 55,000 Philadelphians report to this unit annually and, of these, 40,000 to 45,000 are foodhandlers. Almost two-thirds of the foodhandlers are reporting back, having been x-rayed at least once previously.

The first screening yields about 2 per cent with possible tuberculosis. This figure is a little higher than that reported for many surveys because our photofluorograms are over-read by policy.[2] We believe it is better to err on the side of over-reading than to give false reassurance. This plan was inaugurated because we feel that surveys are screening processes rather than diagnostic procedures.

Routine clinical follow-up after the initial photofluorograms results in a diagnosis of active tuberculosis in about one-half of one per cent, which is in accordance with survey follow-up findings in general.

The shifts from negative to possibly tuberculous on re-x-ray run slightly under half of one per cent. Less than half of these impress the radiologist as probably active tuberculosis. The others are interpreted either as of indeterminate activity or are inactive on the basis of retrospective review.

The following case represents the ideal results obtainable when a chest film reveals active tuberculosis within one year of a negative x-ray film and diagnosis, hospitalization, and good therapy are provided promptly:

Case 1: J.C., a 55 year old white bartender, had a negative photofluorogram February 20, 1948 (Figure 1A). Eleven months later, January 21, 1949 (Figure 1B), his photofluorogram was read: "Moderately advanced active tuberculosis: Infiltra-

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tions in the left infraclavicular region." This man was a diabetic who felt quite well. He had no fatigue, cough, sputum, hemoptysis nor contact with tuberculosis. However, he had lost 35 pounds during the previous 14 months. Positive sputum was obtained on February 9, 1949. Hospitalization was effected on March 9, 1949, and shortly thereafter pneumothorax was induced. Sputum became negative by April 1, 1949. He is well and working with left pneumothorax. His sputum has continued to be negative.

While such excellent results are possible when tuberculosis is found in an early phase, they can only be anticipated if hospital facilities are available and immediate appropriate therapy is inaugurated. The following foodhandler had had two negative photofluorograms before the one which revealed acute tuberculosis. Despite the fact that his tuberculosis was found before he became symptomatic, he died at home without therapy seven months after having been listed for a hospital bed.

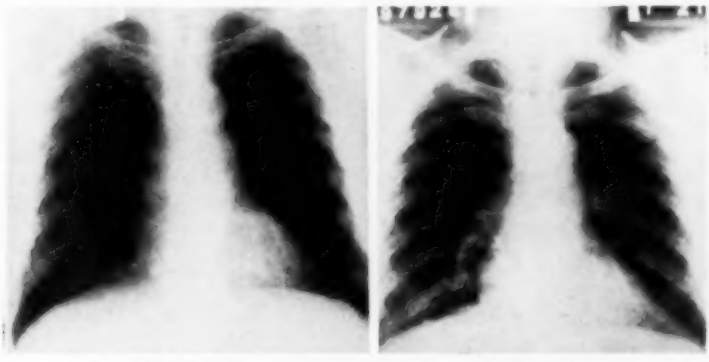

FIGURE 1A FIGURE 1B

Figure 1A, Case 1: February 20, 1948. Negative.—*Figure 1B, Case 1:* January 21, 1949. Infiltrations in the left Infraclavicular region. Sputum positive.

FIGURE 2A FIGURE 2B

Figure 2A, Case 2: March 18, 1948. Negative.—*Figure 2B, Case 2:* June 30, 1949. Dense infiltrations below right mid-lung. Sputum positive.

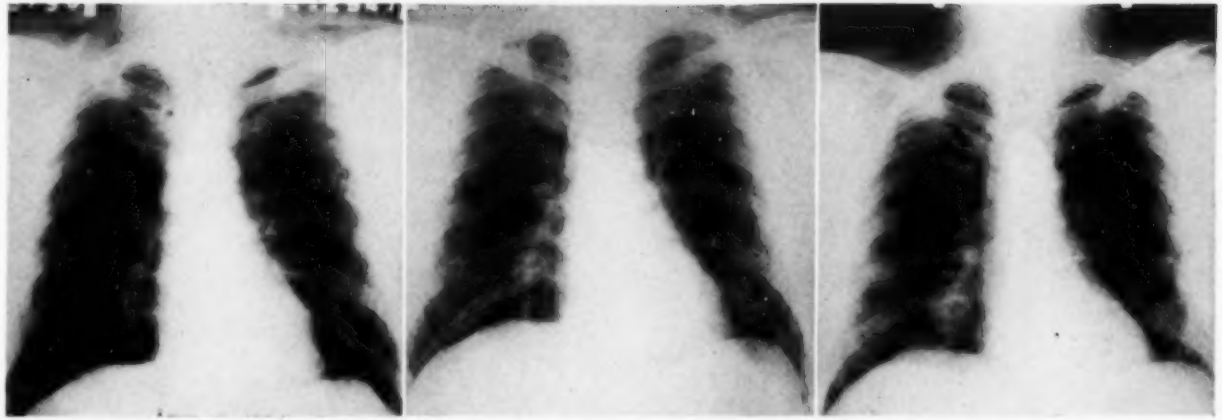

FIGURE 4A FIGURE 4B FIGURE 4C

Figure 4A, Case 5: November 25, 1947. Photogluorogram interpreted as "negative." Retrospective review reveals lesion below right hilum.

Figure 4B, Case 5: February 4, 1949. Mass below right hilum. No symptoms present.

Figure 4C, Case 5: May 21, 1951. Mass below right hilum larger. No symptoms present. Hamartoma removed August 3, 1951.

Case 2: G.W.D., a 47 year old Negro dishwasher, had negative photofluorograms on May 27, 1947, and March 18, 1948 (Figure 2A). On June 30, 1949 (Figure 2B), he had "dense infiltrations below the right mid-lung." No symptoms were present. Positive sputum was not obtained until August 29, 1949. He was listed for hospitalization September 9, 1949, but was never admitted nor treated while awaiting a bed. He died at home April 9, 1950.

Early case-finding can be the magic key to tuberculosis control only if beds for treatment are available. A compromise program of home treatment should be inaugurated while awaiting hospitalization in those localities where bed shortages exist.

The presence of pleural effusion following negative photofluorograms is always highly significant. If it is right-sided and associated with cardiac enlargement, the diagnosis is fairly obvious. If the cardiac shadow is normal, it must be considered tuberculous until proved otherwise. The following two cases are presented as contrasts—the first having received ideal treatment for tuberculous effusion, the second having received inadequate therapy. Obviously, the value of the survey is only as good as the calibre of the subsequent treatment.

Case 3: J.M.G., a 21 year old Negro bus boy, had a negative photofluorogram March 5, 1948. The July 6, 1949 retake revealed a massive right pleural effusion. He was hospitalized July 18, 1949. Re-ray two months after admission revealed left pleural effusion as well as the involvement on the right. Tubercle bacilli were not cultured from the pleural fluid. He was discharged May 8, 1951, to a rehabilitation centre. On January 16, 1952, he reported back for routine check-up. The fluid on the right had completely absorbed and there was only a small amount of residual pleural thickening on the left.

He had long-term adequate treatment. The follow-up picture when treatment is inadequate is illustrated by the following:

Case 4: C.M., a 25 year old Negro porter, had a negative photofluorogram November 24, 1947 (Figure 3A). Two years later, November 3, 1949 (Figure 3B), he had left pleural effusion. Recognizing the gravity of the situation in a young

FIGURE 3A FIGURE 3B

Figure 3A, Case 4: November 24, 1947. Negative.
Figure 3B, Case 4: November 3, 1949. Left pleural effusion.

Negro, immediate hospitalization was arranged. Tubercle bacilli were never isolated from the pleural fluid but streptomycin was given for two and one-half months. He was discharged after only three and one-half months of hospitalization. He was found to be working in a Philadelphia hospital shortly after discharge. This hospital was notified of our concern over the young man's inadequate treatment. X-ray films January 4, 1951, and June 7, 1951, at the hospital showed only thickened pleura but in September, 1951, about two years post-effusion, he developed a large fluctuant mass over the right posterior chest. Material obtained from this area by aspiration yielded tubercle bacilli. The right ninth rib was resected and showed tuberculous osteomyelitis.

This sequence of events is not rare following inadequately treated tuberculous effusion. The experience of the armed forces yielded ample evidence to this effect.[3]

The problems of differential diagnosis are legion. Not only is there the question of etiology but the natural history of tumor growth, suppurative disease, tuberculosis, sarcoid, and other pulmonary diseases unfolds like a panorama before the eyes of the survey reader. The development of pathologic change in patients is demonstrated by the following case in which a "negative" photofluorogram was followed by the appearance of a mass subsequently proved to be a benign tumor. He refused surgery at first until a definite increase in the size of the neoplasm was demonstrated. The period of observation extended over three and one-half years.

Case 5: T.C., a 49 year old white bartender had a photofluorogram interpreted as negative November 25, 1947 (Figure 4A). In retrospect a lesion below the right hilum is visible. On February 4, 1949 (Figure 4B), a round mass was seen below the right hilum. He was asymptomatic and refused the chest clinic's recommendation of hospitalization for diagnosis and treatment. On April 13, 1950, there was doubt as to whether the mass was larger. On May 21, 1951 (Figure 4C), the annual photofluorogram revealed a definite increase in size and the man was persuaded to enter the hospital for surgery. The lesion was a hamartoma.

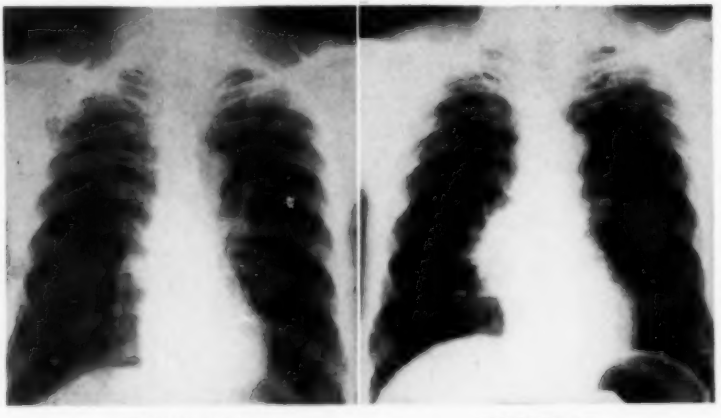

FIGURE 5A FIGURE 5B

Figure 5A, Case 6: April 25, 1947. "Negative." In retrospect there is a questionable rounded density below the right hilum.
Figure 5B, Case 6: April 29, 1948. Mass below right hilum.

Because of the discouraging survival rates in lung cancer, it seems worth while to examine this situation in some detail. There were 49 proved primary bronchogenic carcinomas among 247,060 satisfactory photofluorograms exposed between May 2, 1947, and December 31, 1951. While this represents only two cases per 10,000 individuals, the prevalence for men over 45 was eight cases per 10,000 (38 among 45,887).

It is of interest to note that 30 of the proved cancers had been found on initial photofluorography. Nineteen had had previous photofluorograms read as negative. In retrospect, only 10 of these 19 were truly negative, the balance having had small shadows that had been overlooked. The resectability and survival of these three groups are as follows:

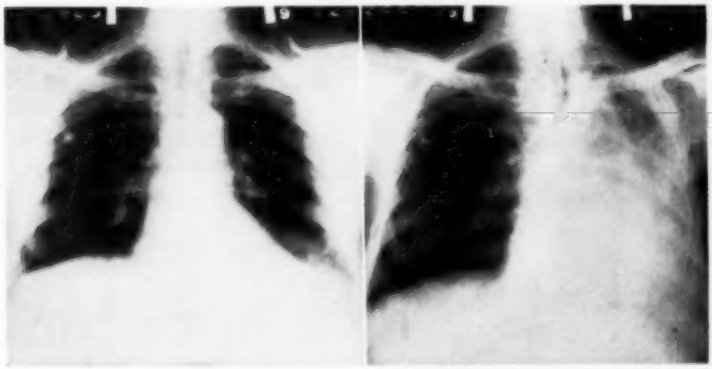

FIGURE 6A FIGURE 6B

Figure 6A, Case 7: September 16, 1950. Essentially negative except for increased basal markings and a calcified nodule at the right third anterior rib.
Figure 6B, Case 7: September 13, 1951. Partial atelectasis left lung. Inoperable. Died October 24, 1951.

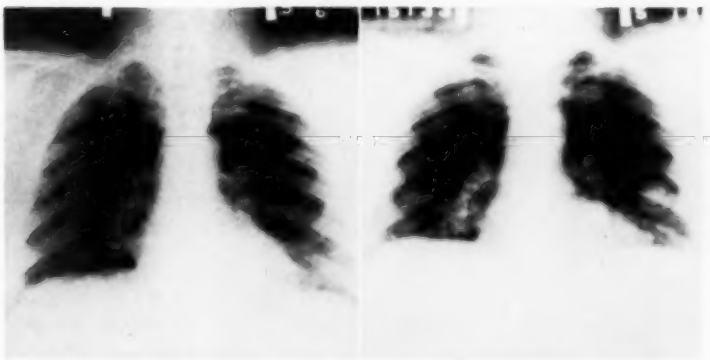

FIGURE 7A FIGURE 7B

Figure 7A, Case 9: May 6, 1947. Negative.
Figure 7B, Case 9: May 18, 1949. Mass left base.

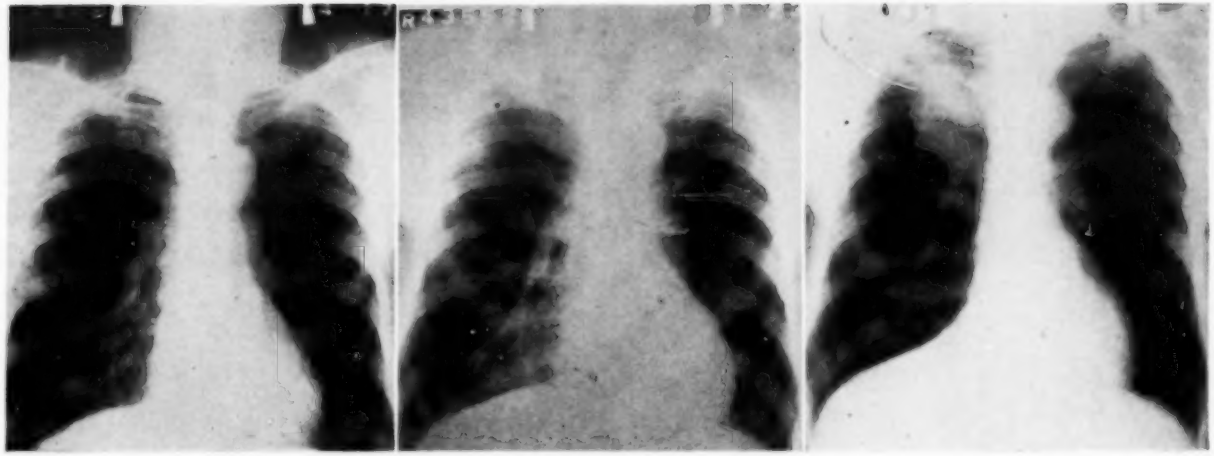

FIGURE 8A FIGURE 8B FIGURE 8C

Figure 8A, Case 10: April 17, 1947. The lesion is present at the level of the third anterior rib.

Figure 8B, Case 10: January 23, 1948. Mass at right second anterior rib (missed by survey reader).

Figure 8C, Case 10: May 28, 1952. Volume shrinkage of right upper lobe.

I. *Those with abnormalities on initial photofluorogram* 30
Resected 8
Living 13 months after resection 1
II. *Those with previous photofluorograms read negative and considered negative even on retrospective review* 10
Resected 4
Living eight months after resection 1
III. *Those with previous photofluorograms read negative but considered abnormal on retrospective review* 9
Resected 5
Living 18 to 45 months after resection 3

It is of interest to note that half of those with available earlier photofluorograms had resectable lesions in contrast to only a quarter of those without previous films. So far as survival is concerned, the study is too recent for evaluation but the advantage of previously "negative" chest x-ray films is apparent when one realizes that five of 19 such individuals are living in contrast to only one of 30 without available previous films.

The following foodhandler, reporting for re-ray one year after a negative photofluorogram, was found to have a mass later proved to be bronchogenic carcinoma. He has survived four years after right pneumonectomy.

Case 6: C.Y., a 55 year old oriental cook, had a "negative" photofluorogram on April 25, 1947 (Figure 5A). In retrospect there is a questionable rounded density below the right hilum. One year later, April 29, 1948 (Figure 5B), a large mass was found below the right hilum. Upon interview May 11, 1948, the only symptom was cough which had been present for years. There was no notation made as to whether there had been recent change in the character of the cough. The man was referred to a chest clinic where he underwent routine examination. After considerable difficulty, he was finally persuaded to enter a hospital on August 16, 1948. The right lung was resected September 9, 1948. He was discharged September 22, 1948. Histologically, the tumor was a squamous cell carcinoma. The patient has returned annually for photofluorograms. The residual lung remains clear and the man continues to work as a cook.

While it is too early to view this as a cure, the case nevertheless presents convincing evidence of the value of periodic chest x-ray films.

On the other hand, the following case highlights the fact that centrally located lung cancers may be silent clinically and negative by routine roentgenography until they are so far advanced as to be inoperable.

Case 7: P.N., a 68 year old white laborer, was referred for photofluorography September 16, 1950 (Figure 6A), by his private physician. The miniature film was essentially negative except for increased basal markings and a calcified nodule at the right third anterior rib. One year later, September 13, 1951 (Figure 6B), he was sent back to the unit by another physician because he had had "pneumonia" of one month's duration. This time there was atelectasis with a shift of the entire mediastinum into the left chest. He was hospitalized October 5, 1951. Bronchoscopy revealed an ulcerating tumor mass involving the left stem bronchus. Both biopsy and cytology yielded a diagnosis of squamous cell carcinoma of the bronchus. Surgery was not feasible because of the patient's poor condition and death occurred October 24, 1951.

The next case reveals the fact that some cancers of the lung have a long history. The following patient's lung was resectable 38 months after photofluorographic abnormalities had been present but missed.

Case 8: J.G., a 61 year old white waiter, had a negative photofluorogram on March 14, 1947, and photofluorograms read negative December 31, 1947, January 7, 1949, and December 24, 1949. In retrospect, lesions at the right base were present in December, 1947, and January, 1949. The abnormalities were not obvious in the December, 1949, film. However, in February, 1951, the abnormality at the right base was finally noted. He was asymptomatic. A right middle lobe lobectomy on March 30, 1951, revealed adenocarcinoma. There was no lymph node metastasis. There has been no evidence of recurrence up to September 12, 1952.

The above patient was cooperative. There are, of course, individuals who simply refuse hospitalization due either to incredulity because of their sense of well-being, fear, or a fatalistic attitude. These problems constitute material for a whole study in themselves. However, there are, unfortunately, instances of delay on the part of physicians. The following is an example:

Case 9: J.L., a 43 year old white proprietor, had a negative photofluorogram on May 6, 1947 (Figure 7A). The photofluorogram of May 18, 1949 (Figure 7B), revealed a mass at the left base. Chest pain had been present in this area for two months. Five months after the presence of this mass was reported we were advised: "Lesion in the left lower lobe larger. In a reasonably short time, he will have an operation." On January 27, 1950, eight months after the abnormal photofluorogram, left pneumonectomy was done but metastasis to a mediastinal node was found. The man died one and one-half years post-operatively.

Just as it is impossible to prognosticate on the basis of a single film with proved tuberculous lesions, so one cannot tell the individual with an intrapulmonary mass how soon he will develop symptoms. The following case demonstrates the unpredictability of neoplastic growth and the fallability of even serial survey readings if photofluorograms are not compared with available previous films. In this instance, incredible as it may seem, the growing mass was only discovered four years after it was visible. The interpretation of areas of homogeneous ground glass density as "negative; thickened pleura" without comparing with previous available photofluorograms nullified the value of serial films.

Case 10: D.S., a 68 year old Negro waiter, had a "negative" photofluorogram in April, 1947 (Figure 8A). In retrospect there was a lesion at the right third anterior rib. The next year, 1948 (Figure 8B), he had a right infraclavicular mass but the radiological interpretation was "negative." Even less credible is the reading of "negative; thickened pleura" on the 1949 film in which the mass was larger. (When a photofluorogram is read "negative," no comparison is made with the previous films.) Again, in 1950, the photofluorogram was read "negative." Finally, in 1951, four years after the mass first appeared, the reader discovered it. At this time the waiter was 72 years old, and had fatigue and cough productive of yellowish, bloodstreaked sputum. Night sweats had been present for a short time. Hospitalization was refused. He continued to work. A photofluorogram taken eight months later, May 28, 1952 (Figure 8C), revealed volume shrinkage of the right upper lung. This man is still working and feels better than he did last year.

It is difficult for radiologists, trained as they are to make every effort at accurate diagnosis, to accept our survey policy of over-reading. Yet, only in this way will the survey screen develop a sufficiently fine mesh to yield maximal benefit.

The following case demonstrates the price one pays for ultra-conservative reading so far as tuberculosis is concerned:

Case 11: J.J., a 49 year old Negro kitchen man, was erroneously read "negative" September 20, 1948, instead of "suspect, right infraclavicular region." February 15, 1950, 17 months later, he had far advanced active disease. He died of tuberculosis six weeks later.

It is unfortunate that undue anxiety may be incurred in individuals suspected of having lesions subsequently found to be innocuous; such anxiety can be minimized by a properly indoctrinated follow-up team of nurses and doctors.[4]

Serial photofluorograms often provide the tuberculosis control officer with the tools necessary to convince the doubting patient of the need for hospitalization. The asymptomatic individual who cannot be convinced of his danger on the basis of a single film can almost always be convinced when shown two or more films which show definite progression.

SUMMARY

Annual chest roentgenograms yield sufficient abnormalities to make them worth while. Like all survey films, they are only as good as their interpretations and subsequent follow-up. Serial film readings can be much more accurate than single film readings if the interpreters take the time to compare previously available photofluorograms. Serious errors can be compounded if readers are casual about classifying lesions.

Tuberculosis found following the existence of previously negative photofluorograms is of graver import than that found in routine first screening for prevalence. Therefore, there is urgent need of facilities for prompt care of these patients or their recently developed acute exudative lesions may progress rapidly to death despite the case-finding efforts. The advent of drug therapy makes it inexcusable to deny these patients treatment.

Serial films provide an opportunity to return to clinical supervision those who have strayed and whose new films reveal progressive disease.

Periodic chest x-ray films furnish a remarkable opportunity to study the natural course of untreated pulmonary disease. Diagnostic problems abound. Even with elaborate study, there always remain a few undiagnosed cases, some of whom regress under our photofluorographic eyes while others progress to a fatal termination.

RESUMEN

Las radiografías de tórax hechas anualmente, proporcionan suficientes anormalidades para que valga la pena hacerlas. Como todas las pesquizas en películs, ésta es tan buena de acuerdo con su eficiente interpretación y prosecusión de los casos. Las series de películas, pueden ser mucho más exactas que la lectura de una sola película si los encargados de estudiarlas se toman el tiempo para comparar todos los fotofluorogramas obtenidos previamente. Se pueden cometer errores serios si los que interpretan las radiografías son informales sobre la clasificación de las lesiones.

La tuberculosis encontrada después de hallazgos previos negativos en radiografías anteriores, es de mayor importancia que la encontrada en las pesquizas radiográficas de rutina. Por tanto, es urgente el tratamiento in-

mediato de estos enfermos o de otra manera, sus lesiones agudas exudativas pueden evolucionar con rapidez hacia la muerte a pesar de los esfuerzos para descubrir los casos. El advenimiento de la terapéutica con las nuevas drogas, hace inexcusable el privar a estos enfermos del tratamiento.

Las películas en serie, proporcionan una oportunidad de volver a la revisión clínica de aquéllos que se han perdido de vista y cuyas nuevas películas revelan enfermedad evolutiva.

Las películas del tórax, periódicamente tomadas proporcionan un medio notable para estudiar la evolución natural de la enfermedad. Los problemas diagnósticos abundan. Aún con el estudio completo siempre quedan algunos pocos casos sin diagnóstico, algunos de los cuales retroceden en su evolución bajo nuestra inspección fotofluorográfica, en tanto que otros, marchan hacia un término fatal.

RESUME

Les radiographies systématiques annuellas du thorax révèlent des anomalies suffisantes pour qu'on les tienne pour indispensables. Comme tous les examens, elles ne sont valables que par leur interprétation et l'examen complet qui lui fait suite. La lecture d'une série de radiographies est bien plus précise que la lecture d'un film unique à condition que les interprètes prennent bien soin de comparer les différents clichés. Des erreurs graves peuvent être faites si les interprètes ne classent pas rigoureusement les lésions.

La tuberculose découverte alors que les clichés antérieurs étaient normaux à une signification infiniment plus importante que celle découverte au premier examen systématique de contrôle. Pour ces malades, il est urgent de mettre en oeuvre avec énergie toutes les possibilités de traitement. Sinon les lésions découvertes récemment arrivent à progresser rapidement jusqu'à la mort. L'apparition de la chimiothérapie rend inexcusable toute négligence de traitement. Les examens systématiques donnent la possibilité de renvoyer à une surveillance clinique les cas douteux et ceux dont les nouveaux films révèlent une évolution.

Les examens en série fournissent une remarquable occasion d'étudier l'évolution naturelle de l'affection pulmonaire qui reste sans traitement. Les problèmes diagnostiques délicats sont nombreux. Même sérieusement étudiés, il reste toujours quelques cas qu'on ne peut diagnostiquer. Certains d'entre eux régressent spontanément, d'aprés les documents radiologiques, tandis que d'autres au contraire progressent jusqu'à la mort.

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Pulmonary Postural Drainage for Bronchiectasis

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Although bronchiectasis is primarily a surgical disease, the patient beyond the help of surgery presents a major problem in its management and treatment. The purpose of this paper is to present simple forms of pulmonary drainage for bronchiectasis which may prove to be a valuable adjunct to accepted therapeutic measures.

A detailed study of methods of postural drainage has been made by the author and no simple method has been found in the literature that appears to be well tolerated by patients. Cecil, in his *Textbook of Medicine* states: "Postural drainage may be accomplished by hanging the head over the edge of the bed until it touches the floor, bending the body sharply over a chair, or markedly elevating the foot of the bed while using no pillows." These methods have been tried and found to be readily abandoned due to inability of the patient to tolerate them. Buckles, in *Surgical Treatment of Bronchiectasis* has used a tilting table and bed. The disadvantage in using the tilting table has been the need for an assistant as well as the inability of the patient to adequately persist in this type of drainage. The expense of this equipment must also be borne in mind. The special bed designed by Buckles helps gravitate secretions; however, it is not as practicable or applicable to every day use as one would desire.

In interviews with patients it was found that the usual method prescribed by physicians is lying over the edge of the bed in the morning with a member of the family helping to hold the patient in bed. This method has not met with success because it results in extreme dyspnea; also, it requires an assistant. The method of hanging over a chair also results in extreme dyspnea and fatigue and is impossible for some patients due to insecurity encountered in such a position.

It has been the experience of the author to find that the above methods, which appear to be most frequently recommended for bronchiectatic patients, are abandoned after a few attempts since they are exhausting, result in headaches, produce dyspnea, palpitation, flushing of the face and inadequate drainage of pulmonary secretions. Patients undergoing such exercises expend much effort in supporting themselves and not concentrating on ridding themselves of the pulmonary secretions. Elderly patients in particular, who are chronic bronchiectatics, find it difficult to assume and continue in these types of pulmonary drainage.

The bronchiectatic patients treated by postural drainage in this series are those who have been found to have moderate to extensive disease, usually on both sides, who are not surgical candidates. These patients may be treated by antibiotic therapy and all other helpful measures, bearing in mind pulmonary postural drainage being of the greatest aid in evacuating the bronchiectatic cavities. It is apparent that these patients will follow

FIGURE 1A FIGURE 1B FIGURE 1C

Figure 1A: Starting position—resting on heels.
Figure 1B: Knee-chest position.
Figure 1C: Resting position.

the advice of a physician who prescribes the most simplified methods of pulmonary postural drainage.

Five years ago the author was afflicted with bronchial asthma. In an effort to eliminate tenacious bronchial mucous plugs at night, it was his experience to note that by lying with three pillows placed underneath the abdomen in a knee-chest position, alternating intermittently in a sitting position in order not to become dyspneic, that adequate pulmonary drainage was easily tolerated. The importance of alternating the knee-chest position and the sitting position cannot be too highly stressed for it was found to be an integral part of the successful accomplishment of the pulmonary drainage since it was efficacious in not causing dyspnea or fatigue. Further studies were done to find simplified and practicable methods for pulmonary drainage and were applied. The results have been most gratifying as attested to by many patients in a period of five years. Four simple methods of pulmonary postural drainage have been utilized in this study.

The best method found by the author has been the knee-chest position. Immediately upon arising, before breakfast, patient is instructed to undergo drainage in this position. It has been found that some patients prefer to move around after arising before undergoing drainage for it has been their experience that "loosening" of the sputum occurs in so doing. A flat surface is to be preferred. A bed is not suitable unless the mattress and spring are very firm and result in no sagging with body weight.

In the knee-chest position, the patient assumes starting position as in Figure 1A, being erect, resting on his heels. This position is then followed by assuming the knee-chest position lying on the forearms with palms outstretched as in Figure 1B. The knee-chest position permits the head and shoulders well below the body of the pelvis and at this stage it is important to pay attention to the thighs being perpendicular to the flat surface of the floor for this permits a greater degree of gravitational drainage of secretions and evacuation of bronchiectatic cavities. As the patient is lying in position, he undergoes several expulsive coughs, expectorating secretions in a disposable paper container.

The importance of the cough being a protective reflex should be explained to the patient at this stage and he should be instructed to breathe in, breathe out, and then cough at the end of expiration similar to the coughing that the physician requires in eliciting post-tussive crepitant rales. The bechic blast with the cough is helpful in eliminating the secretions that lie in the upper tracheobronchial tree. The patient should be instructed to remain only a few minutes in the knee-chest position and immediately thereafter resume resting position as in Figure 1C. The reason for remaining in the knee-chest position only a few minutes is because it has been the author's experience that the patient becomes fatigued, short of breath, face flushes, and as soon as this occurs becomes discouraged and gives up the exercises. If, however, he remains in the knee-chest position for a few minutes and is able to assume resting position as in Figure 1C, he will regain his strength by resting and thus repeat the knee-chest position until such time as he is able to eliminate all secretions.

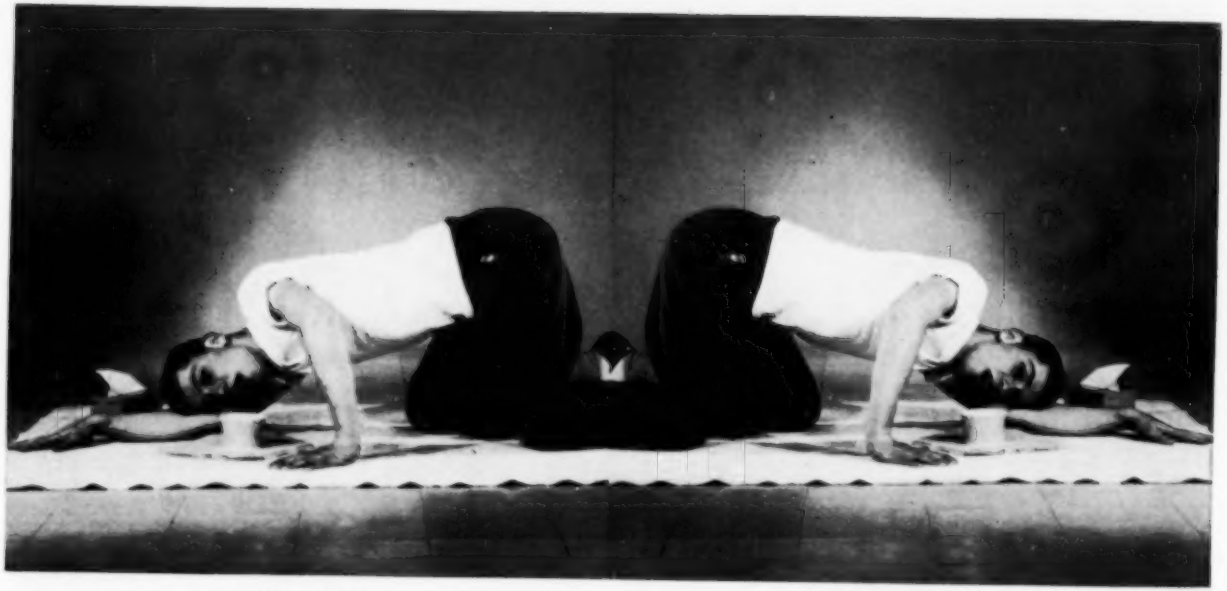

FIGURE 2A FIGURE 2B

Figure 2A: Left lung drainage.
Figure 2B: Right lung drainage.

FIGURE 3A FIGURE 3B FIGURE 3C

Figure 3A: Starting position.
Figure 3B: Elbow-to-knee drainage position, front view.
Figure 3C: Elbow-to-knee drainage position, side view.

FIGURE 4A

FIGURE 4B

FIGURE 4C

Figure 4A: Elbow-to-knee, side view — no chair.
Figure 4B: Elbow-to-knee, front view — no chair.
Figure 4C: Drainage of left lung.

FIGURE 4D

FIGURE 5A

Figure 4D: Drainage of right lung.
Figure 5A: Crouching position.

In an effort to promote more complete drainage of each lung, the patient may partially rotate his trunk in the knee-chest position as in Figures 2A and 2B, lying on the right and left sides respectively. In this position the head rests on the arm and forearm of contralateral lung being drained and the opposite arm is used to help balance the body and rotate it so that the lung being drained is slightly higher permitting secretions to gravitate.

It is noted in literature on bronchiectasis that patients are advised to undergo the strenuous positions described earlier for a half hour several times a day. In the author's experience, each one must be treated as an individual case. Those undergoing knee-chest pulmonary postural drainage exercises are advised to note the quantity and consistency of the sputum daily to see for themselves the gradual reduction in the quantity and change in character from purulent to less purulent and mucoid consistency after a period of days. In pursuing this schedule of exercise for pulmonary toilet, patients are in a better position than the physician to note the amount of time that is required to drain pulmonary secretions. Early in the procedure 15 to 20 minutes may be required, whereas after the exercise has been productive of results only three to five minutes may be necessary. The elimination and reduction of cough and expectoration encourages many persons to adhere to this method of knee-chest position of cleansing the pulmonary tree. The need to be socially acceptable and being enabled to remain on the job is a source of happiness and economic security to many patients. Good drainage also aids appreciably in removal of bad breath when the cause is due to retained pulmonary secretions from bronchiectasis.

Bronchiectatic patients are educated to the fact that daily undergoing of knee-chest exercises for pulmonary postural drainage is a must such as the brushing of the teeth. The physician in charge must pay close attention to details, such as the exact position of the patient and the time he allots to the exercises. Inasmuch as the time interval obviously depends on the degree of bronchiectasis, it has been the experience of some persons to find it unnecessary to continue the exercises every day of the week because of the adequate pulmonary drainage encountered in this method. A group of patients take the exercises only during the days that they feel retained secretions are present and pursue them until such time as all secretions are eliminated and, therefore, undergo intermittent postural drainage alternating with rest periods for a few days. It has been pointed out to these patients that the rest periods must not be too prolonged since they may result in inadequate pulmonary drainage.

Experience has also shown that it is necessary to undergo the exercises throughout the day, depending on the amount of sputum. Patients are required to do the exercises before or between meals and not after eating. The one who diligently undergoes good morning drainage is usually able to go until before the noon meal. The patient who complains of cough and expectoration upon retiring and who states he cannot fall asleep unless he coughs himself to sleep has found distinct benefit in doing the knee-chest pulmonary postural drainage exercises before retiring.

Although the knee-chest exercise has been found to be the best method, daily activities are not always conducive to applying it. For these patients the author has supplemented the elbow-to-knee position. Although it is not as effective as the knee-chest position, it is a very simple method for observation has shown that on occasion persons assume the position without being cognizant of it. In the elbow-to-knee position the patient sits on the end of a chair as in Figure 3A (normal sitting position will not permit flexing of the body forward). With knees flexed, legs apart slightly more than the width of the shoulders, feet firm on the floor, legs perpendicular to the floor, trunk flexed as far downward as possible, patient places elbows in front of knees as in Figure 3B. He then undergoes expulsive cough and bechic blast. Again, the importance of resting, as in knee-chest position, cannot be over-emphasized.

The elbow-to-knee position was found to be more efficient without the aid of a chair for it permits a greater degree of gravity and can be carried out at any time or place. Experience has shown that it requires little practice. Without the chair, elbows rest on the knees; whereas with the chair, elbows are placed in front of the knees. While in this position, the trunk is flexed as far downward as possible as in Figures 4A and 4B and patient undergoes expulsive cough exercises. Again, the importance of rest in an erect posture is stressed. Another advantage without the chair is that it enables drainage of each lung by rotating the trunk downward which is difficult with a chair. It is important to note as in Figures 4C and 4D that one shoulder is lower than the other, elbow of the contralateral lung lies inside the knee and opposite hand rests on knee for support.

For those unable to undergo either the knee-chest or elbow-to-knee positions because of arthritis, deformities of the pelvis or age, the author has devised the crouching position which is done by resting with one forearm and hand on a chair while opposite arm helps support the body on another chair, and bending as far forward as possible by flexing the trunk as in Figure 5A. While in this position, patient undergoes expulsive cough exercises. Periods of rest in these cases, sitting or lying, are important.

Difficulties encountered in these exercises usually arise from misunderstanding and may result in loss of interest with failure to obtain desired results. Repetition of exercises under supervision of physician and re-education promote success. Routinely, the author demonstrates to the patient graphically what occurs in bronchiectasis and during postural drainage. Viewing x-ray films in order to visualize the location of disease enables patient to appreciate the importance of gravity for drainage of secretions. Photographs in this study of a person in postural drainage positions have also been found helpful as a teaching method.

SUMMARY

Four simple methods of pulmonary postural drainage for bronchiectasis have been outlined.

The knee-chest position has been found to be the most successful for it removes a large portion of secretions whenever used.

The elbow-to-knee position with and without the aid of a chair, being simple, supplements the knee-chest for it can be used at any time or place.

The crouching position has been helpful in arthritic and elderly patients.

Experience has proved over a period of five years that patients become expert in the procedure for they are well tolerated, do not require props, assistance or expense.

Helpful aids in individual education are outlined.

These four exercises have been found to be practicable for bronchiectasis as well as other pulmonary diseases requiring drainage, such as tuberculous basal cavities, purulent tracheobronchitis, lung abscess in the lower lobes, bronchial asthma (depending on the severity of dyspnea), asthma complicated by bronchiectasis and pulmonary emphysema. The exercises are also helpful before bronchographic study and surgical procedures requiring pulmonary drainage.

RESUMEN

Se han descrito cuatro métodos sencillos de drenaje postural para la bronquiectasia.

La posición genupectoral, se ha encontrado ser la más efectiva, porque permite expeler gran parte de las secreciones siempre que se usa.

La posición de codos en las rodillas con y sin la ayuda de una silla siendo sencilla, suple a la genupectoral, puesto que puede usarse en cualquier tiempo y lugar.

La posición agachado, es útil en los ancianos y en los artríticos.

La experiencia por más de cinco años, ha demostrado que los enfermos se hacen expertos en los procedimientos porque son bien tolerados, no requieren adminículos, ayuda o gastos.

Se señalan algunas cosas auxiliares en la educación individual.

Se ha encontrado que estos cuatro ejercicios, son practicables para bronquiectasia, así como para otras enfermedades que requieren canalización bronquial, tales como la tuberculosis de las bases, traqueobronquitis purulenta, abscesos de los lóbulos inferiores, asma bronquial (dependiendo de la severidad de la disnea), asma complicada con bronquiectasia y enfisema pulmonar. Los ejercicios son tan bien una buena ayuda antes del estudio broncográfico y de procedimientos quirúrgicos que requieren canalización de secreciones pulmonares.

RESUME

L'auteur insiste sur quatre méthodes très simples de drainage de posture dans les cas de dilatations des bronches. La plus satisfaisante lui à semblé être la position genupectorale, car chaque fois qu'elle à été utilisée, elle à permis l'évacuation d'une grande quantité de sécrétions.

La position coude aux genoux, avec ou sans l'aide d'une chaise est un simple complément de la position genupectorale car elle peut être utilisée n'importe quand et n'importe où.

La position accroupie à été très utile chez les malades arthritiques ou âgés.

L'expérience à montré, à la suite de cinq années d'essais que les malades eux-mêmes acquièrent une grosse expérience dans les procédés qu'ils supportent bien, et qu'ils n'ont besoin d'aucune assistance particulière.

L'auteur insiste sur l'aide efficace que comporte l'éducation de chaque malade.

Ces exercices ont semblé utilisables aussi bien pour les dilatations des bronches que pour les autres affections pulmonaires nécessitant un drainage (cavernes tuberculeuses de la base, trachéo-bronchites purulentes, abcès du lobe inférieur, asthme bronchique avec dyspnée importante, asthme compliqué de dilatation des bronches, emphysème pulmonaire). Ces exercices sont également d'un grand intérêt avant bronchographie, et avant les actes chirurgicaux nécessitant un drainage pulmonaire.

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Obstruction of the Esophagus by Diseased Ectopic Gastric Mucosa*

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In the past decade, advances in anesthesiology, antibiotics, pre- and post-operative care and surgical technique have greatly increased the scope of thoracic surgery. Among those profiting by these advances, is the individual suffering from esophageal obstruction.

Recently reported benign lesions producing esophageal obstruction include acylasia, chemical obstruction, congenital obstruction, webs, congenital strictures, perforation (spontaneous and traumatic) and fistulae. It is our purpose to present two cases of esophageal obstruction due to diseased ectopic gastric mucosa and to emphasize the desirability of carefully evaluating the cause of obstructive lesions in order to remove the possibility of overlooking a non-malignant lesion. Inasmuch as diagnosis of such lesions today is often based upon direct visualization by esophagoscopy and by barium studies, it is possible to believe that some so-called malignancies of the esophagus are in truth quite benign and amenable to surgical correction. It has been the experience of many thoracic surgeons and pathologists that repeated attempts at biopsy of such lesions have failed to prove the presence of a cancer. In such instances, the clinical diagnosis of carcinoma, although unsupported, often prevails and is accompanied by unjustified pessimism. On the basis of the following two cases it is believed that a more detailed study of possible benign lesions of the esophagus is mandatory.

Ectopic gastric mucosa is not an infrequent finding. It has been reported in the upper third of the esophagus,[14,17] the lower third of the esophagus,[10,14,18] within gastric cysts of the mediastinum,[3,4,13,16] chronically inflamed gall bladders, cysts of the pancreas, Meckel's diverticula[1,2,5,6,8,9,11,15,17] chronic tuberculous ulcers of the colon[6] and in teratomas. These islands of gastric mucosa, no matter where they may occur, are subject to all the diseases and malformations to which gastric mucosa is heir. These include acute and chronic inflammations, ulcerations, polypoid hyperplasias, and hypertrophies. When symptoms arise from such ectopic foci, they usually are due to ulceration of the focus with subsequent hemorrhage and/or pain. In each of the cases presented here, however, the primary symptom was esophageal obstruction which later proved to be caused by ectopic foci of gastric mucosa which had become diseased.

Case 1: A 45 year old white female entered the hospital because of vomiting and dysphagia which had its onset six months prior to admission and was

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accompanied by a sensation of food lodging in the lower esophagus. This condition became progressively worse until two weeks prior to admission, at which time two attempts at esophageal dilatation were made. These afforded some relief but on the day prior to admission she became much worse, was nauseated, vomited and could retain only fluids.

History and physical examination were essentially negative. She showed no evidence of weight loss. Routine laboratory studies were normal. Esophagograms showed a sharply outlined obstruction at the junction of the middle and lower thirds of the esophagus (Figure 1). On November 1, 1951 esophagoscopy was performed and an obstructing lesion was seen 30 cm. from the gum margin. A biopsy was obtained and bougies were passed in an attempt to dilate the obstruction. The pathologic diagnosis of the biopsy specimen was esophagitis, ulcerative, severe. The inflammatory reaction was so severe that the tissue pattern was destroyed and much of the specimen consisted merely of fibrino-purulent exudate. No specific epithelium was identifiable.

The pathologist in his report made a supplementary comment that from the

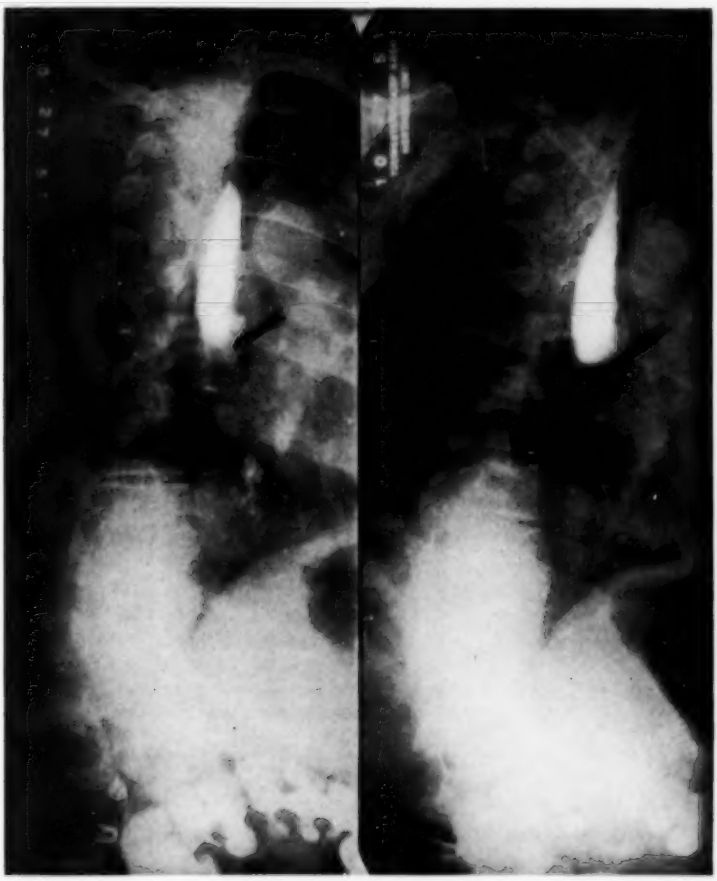

FIGURE 1 (Case 1): Esophagograms demonstrating an esophageal obstruction at the junction of the middle and lower thirds of the esophagus.

microscopic appearance the lesion might possibly be ectopic nests of gastric mucosa. On November 6, 1951 the endoscopic examination was repeated, and a second biopsy was obtained (Figure 2). This was reported as, "1. Gastric mucosa, ectopic, polypoid, of the esophagus. 2. Esophagitis, chronic, ulcerative, severe. 3. Esophagitis acute, focal, severe."

With each of the endoscopies, attempts had been made to dilate the esophagus, but these had not been successful. An exploratory thoracotomy was advised.

On December 7, 1951 with the patient in the conventional left lateral position, the thorax was opened. After the rib spreader had been placed, the pulmonary ligament was dissected up to the level of the inferior pulmonary vein. The mediastinal pleura was then opened and the esophagus mobilized. The wall of the lower 8 cm. of the esophagus was found to be markedly thickened and adherent to the surrounding structures. After freeing up the involved area, the esophagus was incised in a longitudinal direction. The lumen was completely obstructed. A biopsy of the entire thickness of the wall was taken, and submitted for frozen section. The report on the biopsy was as follows, "Esophagitis chronic and acute, ulcerative, severe. Hyperplasia polypoid, adenomatous, of ectopic gastric mucosa within the esophagus." The diaphragm was then opened, and the lower segment of the esophagus was resected. Examination disclosed characteristic gastric mucosa (Figure 3). An anastamosis between the fundus and the esophagus was carried out without difficulty. Further details of the operation technique have been omitted because they have become standardized. Her post-operative course was uneventful.

Case 2: A 54 year old white female experienced difficulty in swallowing for six months. This had its onset one month following cholecystectomy. The dysphagia consisted of an uncomfortable low substernal sensation on swallowing solid food. This was relieved by liquids. These symptoms persisted and progressed to the point where only liquids could be taken. There had been a 30 pound weight loss, during this period. Routine laboratory studies were essentially negative. Esophagograms revealed an obstructing lesion of the esophagus in the lower third (Figure 4).

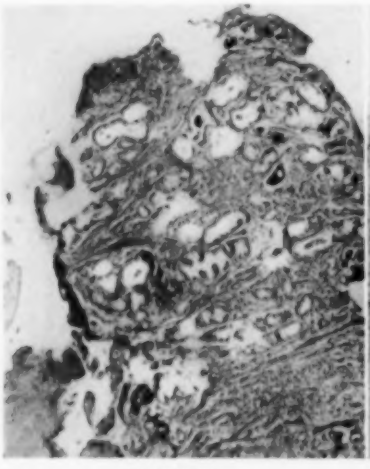

FIGURE 2

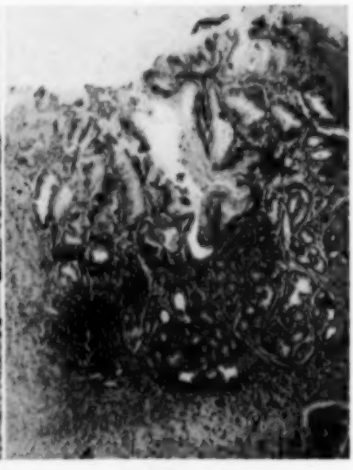

FIGURE 3

Figure 2 (Case 1): Photomicrograph (x 100) taken of second esophageal biopsy, showing typical gastric mucosa with adjacent nest of squamous epithelium.—*Figure 3 (Case 1):* Photomicrograph (x 100) taken of resected segment of esophagus.

FIGURE 4 (Case 2): Esophagogram showing persistent filling defect and obstruction of the lower third of the esophagus.

FIGURE 5 (Case 2): Gross specimen. Resected portion of esophagus showing polypoid, hemorrhagic gastric mucosa.

FIGURE 6 FIGURE 7 FIGURE 8

Figure 6 (Case 2): Photomicrograph (x 50) of esophageal biopsy. In this instance the entire tissue is partially autolysed and disintegrating. Outlines of tubular structures can be seen but the character of their composition is uncertain and this, no doubt, accounts for the erroneous diagnosis of hemangioma.—*Figure 7 (Case 2):* Esophagus at time of operation. Esophagus has been opened, exposing the hemorrhagic polypoid structure which obstructed the lumen.—*Figure 8 (Case 2):* Photomicrograph (x 50) showing transition from normal esophageal epithelium to ectopic polypoid gastric mucosa.

There was no evidence of congenitally short esophagus or of a hiatus hernia in either case.

On November 9, 1951 diagnostic esophagoscopy was carried out. There were accumulated secretions all the way down. After aspirating the secretions, a brief view was obtained of what appeared to be a tumor mass, but contact of this area with the suction tip produced severe bleeding. The bleeding continued and the lesion could not be revisualized. On November 13, 1951 esophagoscopy was repeated and this time the lesion was well visualized. It had the appearance of a very injected polyp (Figure 5). Biopsy was obtained which was reported as follows, "Hemangioma of the esophagus" (Figure 6). An exploratory thoracotomy was advised.

She was prepared in the usual fashion and on December 6, 1951 thoracotomy was performed as described in the previous case. After mobilizing the esophagus, an area similar in length to that of the previous case was encountered. Again the esophagus was opened longitudinally and complete obstruction was present (Figure 7). Biopsy and frozen section revealed "ectopic gastric mucosa." This was subsequently confirmed on the permanent section (Figure 8). Resection and anastamosis was carried out as in the previous case (Figure 5). The immediate postoperative course was uneventful. Eight weeks post-operatively she had difficulty swallowing solid foods. She was again esophagoscoped. The site of the anastamosis appeared normal but somewhat narrowed. This was easily dilated. Subsequent dilatation was required on one other occasion.

Both cases are now doing well.

Discussion

In the first case, the lesion covered a large area showing peptic ulceration, cicatrization, and stenosis. In some places gastric mucosa was preserved but in other areas the ulceration had completely destroyed the usual mucosal structures. This process can be so extensive as to obliterate completely all semblance of the gastric mucosa. By virtue of the histopathologic processes, however, it is possible in many instances to consider ectopic gastric mucosa as an underlying factor in so-called widespread ulcerative, necrotizing esophagitis. Recently we have had a third case which was initially thought to be due to gastric mucosa. However, following resection of the stenosed area, it was found that the ulceration involved the entire surface and that it was no longer possible to identify the epithelial structures.

In the second case, the obstruction was due to polypoid hyperplasia of gastric mucosa. It is, by analogy, reasonable to suppose that within such islands of gastric mucosa, changes could occur similar to those within the stomach or Meckel's diverticula. The mechanical obstructing component of the disease in the esophagus, however, is far more important than in either of the lower locations.

Inasmuch as these lesions will mimic malignancy by virtue of their clinical signs of obstruction, weight loss, pain, bleeding, and x-ray patterns, we feel that the surgeon should possess conclusive proof of the essential malignancy of the lesion before he admits defeat. In the absence of positive histologic evidence of cancer, repeated attempts to establish a precise diagnosis should be made. If, after reasonable attempts, a diagnosis has not been established, the patient should be given the benefit of an exploratory thoracotomy.

SUMMARY

1) Two cases of esophageal obstruction due to diseased ectopic gastric mucosa are reported.

2) On the basis of these and similar cases, it is urged that the obstructive lesions of the esophagus should never be classified as malignant on a basis of clinical, roentgen, and endoscopic appearances alone. If definite histologic proof is not otherwise available, the patient should receive the benefit of surgical exploration.

RESUMEN

1) Se refieren dos casos de obstrucción del esófago debida a mucosa gástrica ectópica.

2) Sobre la base de estos y de casos similares es preciso que las lesiones obstructivas del esófago no sean clasificadas como malignas apoyándose en las apariencias clinica, radiológica y endoscópicas solamente. Si no se obtiene una prueba histológica concluyente el enfermo debe beneficiarse de una exploración quirúrgica.

RESUME

1) L'auteur rapporte deux cas d'obstruction oesophagienne dus à une ectopie pathologique de la muqueuse gastrique.

2) En se basant sur ces deux cas, et sur d'autres similaires, il est de première importance de savoir que le diagnostic de cancer ne doit pas être fait en présence d'obstruction oesophagienne, sur les seuls caractères clinique, radiologique ou endoscopique. Si par ailleurs, la preuve histologique ne peut être apportée d'une façon valable, il ne faut pas hésiter à faire bénéficier le malade de la chirurgie exploratrice.

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Clinical Differentiation of Pulmonary Infarction

(Correlation of Clinical and Pathologic Findings)

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On the medical service of a neuropsychiatric hospital the clinical diagnosis of acute pulmonary infarction can be especially difficult. Most psychotic patients cannot relate good histories. Evaluation of symptoms and of signs is fraught with obstacles. The classical syndrome of chest pain, hemoptysis, consolidation of lungs, friction rub, and shock may not be present. The laboratory studies are at times of questionable value; the electrocardiogram may be misleading, particularly if it is used as the sole differentiating criterion; and the x-ray studies too may be confusing.[1] The problem is further complicated because this lesion may coexist with or follow pneumonia or other serious illness. In order to determine the factors which might aid in the clinical diagnosis of pulmonary infarction, we have reviewed the pathological material at this hospital during the five year period January 1, 1947 to December 31, 1951; and correlated it with the clinical findings.

In that period there were 391 deaths and post-mortem examinations were performed in 255 instances. In 19 cases, there was pathologic evidence of pulmonary tissue necrosis with either pulmonary arterial embolism, pulmonary arterial thrombosis, or both; in short, there were 19 male patients with pulmonary infarction. This incidence of 7.4 per cent is in agreement with figures of Katz[2] et al and of Belt, cited by Katz.

Eighteen of the patients were white and one was a negro. No statistical significance is attached to this finding because the majority of post-mortems were on white people.

Table I lists the psychiatric diagnoses established for 13 of our patients prior to death. There were also six without psychiatric diagnoses.

In our series the age distribution is shown in Table II. The majority (58 per cent) were in the 51 to 60 age group.

Two of the 19 infarctions developed post-operatively: one, nine days post-cholecystectomy (after leaving bed the first time); the other, 21 days after gastric resection (in a patient still confined to bed). One suffered

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From the Medical Service of the United States Veterans Administration Hospital, Lyons, New Jersey; published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

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†Chief of Service.

TABLE I

Schizophrenia	4
Psychosis with arteriosclerosis	2
Psychosis with central nervous system, syphilis	1
Psychosis with arteriosclerosis and central nervous system, syphilis	1
Psychosis with alcoholism	1
Psychosis with grand mal epilepsy	1
Psychosis with multiple sclerosis	1
Manic depressive psychosis	1
Psychopath	1

TABLE II

41-50	1	
51-60	11	(58 per cent)
61-70	5	
71-80	2	

from aplastic anemia, which was confirmed by repeated bone marrow studies for a year, before developing infarction. One was thought to succumb to a cerebral thrombosis. Three were considered to have terminal pneumonia, one of whom was believed to have colon carcinoma with pulmonary metastases in addition to the pneumonia.

The remaining 12 had clinical evidence of heart disease. One had rheumatic heart disease; three hypertensive cardiovascular disease; and eight had arteriosclerotic heart disease. The detailed cardiac diagnoses are listed in Table III.

TABLE III

Rheumatic heart disease with bacterial endocarditis
Hypertensive cardiovascular disease
Hypertensive cardiovascular disease and pulmonary tuberculosis
Hypertensive renal disease with cardiac failure
Arteriosclerotic heart disease; acute myocardial infarction
Arteriosclerotic heart disease; cardiac failure (two cases)
Arteriosclerotic heart disease; cardiac failure, pneumonia
Arteriosclerotic heart disease; cardiac failure, saddle aortic embolus
Arteriosclerotic heart disease; pneumonia
Arteriosclerotic heart disease; pneumonia, pulmonary tuberculosis
Arteriosclerotic heart disease; pneumonia, decubitus ulcers

One patient developed pulmonary infarction shortly after leaving bed for the first time on the ninth day after operation. The other 18 *had been in bed* for many days prior to the onset of pulmonary infarction.

Eleven expired within 24 hours of the onset of the terminal syndrome; three in shock and eight in coma. The remaining eight lived longer than 24 hours, and as might be expected from the duration of their illness, seven became comatose while only one died in shock.

Pneumonia was diagnosed ante mortem in seven cases but was confirmed post-mortem in only three. Heart disease was diagnosed ante mortem in

12 cases but was confirmed post-mortem in only 10. However, six additional unsuspected cases of heart disease were found at autopsy. Thus, there were 16 of the 19 with heart disease antedating pulmonary infarction. The types of heart disease found at post-mortem are listed in Table IV.

TABLE IV

Arteriosclerotic heart disease	13
Rheumatic heart disease	4
Congenital	1
Cor pulmonale (secondary)	1

Nine patients exhibited thrombo-embolic phenomena at sites other than the lungs. The sites and relative frequency are listed in Table V. The table reveals that four had intracardiac mural thrombi, three had prostatic venous thrombosis; and one had inferior vena cava thrombosis.

TABLE V

Intracardiac mural	4
Prostatic venous plexus	3
Aorta	2
Spleen	2
Femoral artery	1
Iliac artery	1
Mesenteric artery	1
Inferior vena cava	1
Liver	1

Five had neoplastic disease; of these, two were diagnosed ante-mortem* and three at time of necropsy. They are listed in Table VI.

TABLE VI

*Carcinoma of tongue	1
*Carcinoma colon of colon with metastases to lungs	1
Carcinoma of colon	1
Carcinoma of pancreas	1
Meningioma	1

Discussion

There is an idea prevalent in the literature and exemplified by White[3] that psychotic individuals, particularly schizophrenics, rarely have heart disease. Unpublished data from this hospital[4] indicate that schizophrenics suffer from heart disease at least as frequently as do the general population. Our data indicates that during the period considered there were 133 post-mortem examinations on psychiatric patients. The diagnosis was schizophrenia in 36 per cent. Table I indicates that there were four schizophrenics who developed pulmonary infarctions. We should like to emphasize that pulmonary infarction is not rare in schizophrenics.

In 1947-48, one of us[4] studied 1,172 psychotic patients in this hospital; those in the age group 51 to 60 numbered 666 (57 per cent). Our data (Table II) indicates that 58 per cent of the infarctions occurred in this same age group. Age per se does not appear to be an etiologic factor in pulmonary infarction since the proportion in the 51 to 60 range was found to be similar in the hospital population and in the present study (vide supra).

Although pneumonia was diagnosed ante-mortem in seven casis it was confirmed only in three. Since the clinical and laboratory findings are often similar, the two conditions are frequently confused. When an elderly patient confined to bed develops the clinical picture of pneumonia, it is necessary to exclude pulmonary infarction.

During the period, considered the gross autopsy incidence of heart disease at the hospital, among the psychotic patients, was 71 per cent.[4] In our group with pulmonary infarction, the gross autopsy incidence of heart disease was 84 per cent. This is considerably greater than the 30 per cent implied by Katz and Walsh in citing data of Hampton and Castleman.[2]

Disease of the heart itself may not play a role in the causation of pulmonary infarction but we feel, as do Musser[5] and Moran[6] that cardiovascular disease in general predisposes to thrombo-embolic phenomena. This may be particularly so with regard to atherosclerosis. It may be a coincidence but in our 19 cases with pulmonary infarction not one evidenced stigmata of syphilitic cardiovascular disease at autopsy, yet during this same period 19 per cent[4] of those with heart disease evidenced at post-mortem had lesions of syphilitic cardiovascular disease. This absence of syphilitic cardiovascular disease in our group may be related to pathogenesis. In syphilis the tunica media is involved, particularly in the proximal ascending aorta; while in atherosclerosis the intima is more involved. Perhaps the intimal lesions predispose more to thrombus formation, than do primary medial lesions.

In our 19 patients 18 had been in bed many days before the onset of pulmonary infarction and one developed infarction shortly after leaving bed the first time in nine days. Immobilization in the supine position is a predisposing factor. This is in agreement with current thought.[6]

Neoplasms were found in five (26 per cent) patients with pulmonary infarction, but in only 16 per cent of all the autopsies on psychotic patients done during the same period.[2] Although this is a small series; it may be that neoplastic disease predisposes to thrombo-embolic disorders.

SUMMARY

1) Nineteen patients with pathologic evidence of pulmonary infarction were studied in a neuropsychiatric hospital.
2) Clinical and pathologic diagnoses were correlated.
3) The occurrence of pulmonary infarction in psychotic individuals is not uncommon.
4) Certain predisposing factors were elicited.
5) Pulmonary infarction and pneumonia are often confused clinically.

6) Cardiovascular disease, posture, and neoplasms appear to play significant roles in the causation of pulmonary infarction.

RESUMEN

1) En un hospital de psiconeuróticos, se estudiaron diecinueve enfermos con evidencias de infarto pulmonar.
2) Los diagnósticos clínico y patológico, se correlacionaron.
3) La frecuencia del infarto pulmonar en los sujetos con padecimientos psicóticos, no es fuera de lo común.
4) Se descubren ciertos factores predisponentes.
5) El infarto pulmonar y la neumonía, son a menudo confundidos clínicamente.
6) Parece que las enfermedades cardiovasculares, las posiciones, y las neoplasias, desempeñan papel importante para causar los infartos del pulmón.

RESUME

1) L'auteur étudie dans un hôpital neuro-psychiatrique 19 malades atteints d'infarctus pulmonaire certain.
2) La clinique et l'anatomie pathologique se montrèrent d'accord.
3) La survenue d'infarctus pulmonaire chez les individus atteints de troubles mentaux n'est pas exceptionnelle.
4) L'auteur à éliminé certains facteurs prédisposants.
5) Il y à souvent confusion entre infarctus pulmonaire et pneumonie.
6) Les affections cardio-vasculaires, le décubitus prolongé, et les affections néoplasiques paraissent jouer un rôle important dans l'étiologie de l'infarctus pulmonaire.

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The Reversibility of Pulmonary Overdistention

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The problems of treatment posed by total pneumonectomy have always been two-fold. First, the creation of a large dead space was contrary to a cardinal principle of surgery. Secondly, the fate of the "good lung" from both the physiological and pathological standpoint, has been the subject of conjecture.

The problem of a large dead space appeared frightening to Graham[1] when he performed his first pneumonectomy. He solved this problem by performing a concomitant thoracoplasty to obliterate it. By so doing, he doubtlessly minimized overdistention of the remaining lung and thus solved the second problem in a satisfactory manner.

Gaensler and Strieder[2] have shown that early thoracoplasty appears more valuable than late thoracoplasty from a function-sparing standpoint but indicate that thoracoplasty per se, even over a dead space, results in some functional loss. Nevertheless, Strieder[3] believes that post pneumonectomy thoracoplasty is a worth-while procedure, if only to prevent annoying cough and make the patient more comfortable.

It is generally agreed upon that prevention of overdistention is desirable. This is so, especially, since the results of treatment, when overdistention has become clinically established, are not satisfactory.

Furthermore, no standardized method of correction of overdistention has been evolved. Various authors have advocated thoracoplasty, pneumothorax, oleothorax, and procedures employing plombage in an effort to allow the mediastinum to stabilize in its normal position in the midline. On the other hand there are surgeons who do not employ post-pneumonectomy space obliterating procedures to preserve function. They believe overdistention is only dangerous in the tuberculous patient where it may result in breakdown of foci in the opposite lung.

It was surprising to us to find[4,5] that few statistics were available to document the clinical improvement often seen following treatment for well established postsurgical compensatory emphysema. The following case histories are presented to substantiate the authors' impression that the often striking amelioration of symptoms following treatment of pulmonary overdistention must have some basis in fact.

Case 1: A 54 year old white male who had undergone right pneumonectomy for bronchogenic carcinoma two years prior to the time he was first seen by us. The operating surgeon had not performed a thoracoplasty because he believed he had not achieved a cure and felt that the patient would not experience incapacitating ventilatory difficulties within his predicted life expectancy. The patient was hospitalized because of extreme shortness of breath on mild exercise. His maximum breathing capacity was 19 liters per minute; his walking ventilation was 16 liters per minute. The mediastinum was retracted entirely within the right chest and there was a severe overdistention of the remaining left lung. Pneumoperitoneum was instituted; the initial amount of air was 2,000 cc's. He received refills at four

day intervals thereafter for two weeks. He experienced marked symptomatic relief of dyspnea and at the end of this time his maximum breathing capacity was 44 liters per minute and his walking ventilation was 15 liters per minute. The patient did not tolerate pneumoperitoneum well and had much abdominal discomfort with it. He refused to take further treatment.

Comment: The maximum breathing capacity increased 130 per cent after pneumoperitoneum induction. This excellent result obtained despite a well established compensatory emphysema of over two years duration.

Case 2: A 28 year old white male who had undergone right lower lobectomy three years prior to the time we first saw him. Because of postoperative complications with an unexpendable right upper lobe the pneumonectomy was completed approximately one month later. Because of the emotional instability of this patient plus the fact that he had become addicted to drugs, the operating surgeons decided against the performance of a thoracoplasty. Examination revealed that he was extremely short of breath. His mediastinum was retracted into the right hemithorax and there was marked overdistention of the left lung. His meximum breathing capacity was 24 liters per minute and his walking ventilation was 18 liters per minute. It was felt that thoracoplasty would conceivably help but in light of his previous behavior following surgery it was thought hazardous. Pneumoperitoneum was initiated and followed with refills at three day intervals until it became stabilized. At the end of 10 days his maximum breathing capacity was 38 liters per minute and his walking ventilation was 15¼ liters per minute.

Comment: The 58 per cent increase in the maximum breathing capacity was accompanied by a two and one-half liter drop in the walking ventilation indicating increased ventilatory efficiency.

Case 3: A 38 year old white male who was admitted to the hospital with severe hemoptysis. Subsequent workup revealed bronchiectasis of all segments in the left lung and, in addition, there were asthmatic type wheezes present throughout the entire right lung. This patient's maximum breathing capacity was 36 liters per minute and his walking ventilation was 16 liters per minute. It was felt that he should undergo left pneumonectomy but the condition of his other lung posed a serious problem as far as its ability to carry the breathing load was concerned. Differential bronchospirometry showed that 85 per cent of his function was obtained from his right lung and 15 per cent from his left lung. He was given a short course of ACTH which increased his maximum breathing capacity to 46 liters per minute. The asthmatic wheezes were no longer present in the right lung. He underwent left pneumonectomy and 10 days following his maximum breathing capacity was 39 liters per minute. He was advised to have thoracoplasty on his left side but he refused to give permission for this operation. Two months following surgery x-ray films revealed that the mediastinum had shifted considerably to the left side. No asthmatic wheezes were present on the right side but he began to experience shortness of breath on mild exercise. Maximum breathing capacity was 32 liters per minute. He finally gave consent to have thoracoplasty performed and seven ribs were subsequently removed subperiosteally. Six weeks postthoracoplasty his maximum breathing capacity was 44 liters per minute and his walking ventilation was 15 liters per minute and he was able to perform relatively strenuous activity without being short of breath.

Comment: This patient illustrates the often abrupt onset of compensatory emphysema following pneumonectomy. His prompt improvement following thoracoplasty at a relatively early postpneumonectomy date was gratifying.

Case 4: This 42 year old white female had undergone a radical mastectomy on her left side in 1948 for carcinoma of the breast. She was treated with deep x-ray immediately after operative convalescence and has remained essentially well until June 1951, when she developed cough productive of purulent secretions, shortness

of breath, anorexia and weight loss. These symptoms became progressively worse and she was first seen by us in the midle of July 1951. Examination at that time revealed a destroyed left lung and subsequent workup failed to reveal evidence of metastatic disease. It was felt that she suffered severe radiation damage to the left lung and left pneumonectomy was advised. Surgical specimen revealed diffuse interstitial pulmonary fibrosis and fibrous obliterative endarteritis—both consistent with irradiation fibrosis. No attempt was made to obliterate the postpneumonectomy space.

Prior to pneumonectomy the vital capacity was 1.2 liters or 41 per cent of predicted normal. A vital capacity in three seconds was 1.1 liters or 92 per cent of her total vital capacity. Six months postpneumonectomy her vital capacity was 1.3 liters and her three second vital capacity was 1.1 liters indicating no loss of function following the surgical procedure. Despite this finding, she stated that she had become short of breath and x-ray films revealed the trachea to be shifted considerably into the left chest. Dyspnea persisted and she became troubled with chronic, although non productive, cough. These symptoms persisted and it was decided to perform thoracoplasty in an attempt to alleviate dyspnea. This was done in July of 1952, when a limited five rib upper thoracoplasty was performed. She made an uneventful convalescence and stated that her breathing was markedly improved. Ventilatory studies carried out four months postthoracoplasty revealed that her vital capacity was 1.3 liters; that her one-second vital capacity was 0.4 of a liter and that her three-second vital capacity was 1.1 liters. Her maximum breathing capacity was 40 liters per minute and her air velocity index was 0.92. At the time of these studies she was free of cough and had no dyspnea carrying out her normal activities.

Comment: No significant change in measureable function occurred at any stage of this patient's course yet dyspnea was no longer a problem following thoracoplasty. Whether the relief of dyspnea was due to the disappearance of cough, or whether another mechanism which proceduces dyspnea—immeasurable from a function standpoint— is present, is open to conjecture.

Case 5: This 63 year old white male consulted us for extreme shortness of breath. He had been told that he had pulmonary tuberculosis and was retired from his job 10 years ago for this reason. Subsequently he had been treated for "asthma".

X-ray films revealed both upper lobes to be markedly contracted and fibrosed with associated compensatory emphysema of severe degree. The supraclavicular areas were deeply retracted. Fluoroscopy revealed poor diaphragmatic and rib cage motion and laboratory studies showed the presence of acid fast organisms in the sputum.

The vital capacity was 2 liters or 45.5 per cent of the predicted normal. The vital capacity in three seconds was 1.2 liters or 60 per cent of the total. He was short of breath and had great difficulty in walking even a short distance on a flat surface.

Bronchoscopy revealed marked upward retraction of both upper lobe bronchi. The segmental divisions of the left lower lobe could not be visualized due to marked distortion of the bronchial tree secondary to contraction of the left upper lobe.

It was felt that he was not a suitable candidate for definitive treatment of his bilateral upper lobe fibroid tuberculosis and, therefore, pneumoperitoneum was induced solely to alleviate his severe compensatory emphysema.

Following induction of pneumoperitoneum he noted considerable improvement in ability to breathe. He was subsequently discharged to a sanatorium where pneumoperitoneum refills were maintained. Two months following the induction of pneumoperitoneum his vital capacity was 2.5 liters or 58 per cent of predicted normal. His vital capacity in one second was 0.7 of a liter and in three seconds 1.8 liters (72 per cent of total vital capacity).

Comment: This patient has experienced a 25 per cent increase in vital capacity and 50 per cent increase in three second vital capacity, following the alleviation of some of his compensatory emphysema. Although he had no surgery it is felt that the problem of overdistention secondary to shrunken lobes is essentially the same phenomenon noted in postpneumonectomy overdistention.

Discussion

Overdistention of the lung can and does occur whenever there is loss of lung substance following extirpative surgery. It may also occur with loss of lung substance from diseased states. It is a problem more in degree than in kind, and presents symptoms only when the loss of lung substance is relatively large. In the postpneumonectomy state there is often a considerable increase in the lung volume of the remaining lung and this increase is roughly parallel to the increase in the residual air.[2]

There is evidence[6] to show that the development of scoliosis after thoracoplasty results in a marked decrease in ventilatory function. On the other hand, maintenance of pneumothorax in the postpneumonectomy space entirely prevents overdistention and conversion of pneumothorax to oleothorax apparently causes no alteration of pulmonary function or lung volume.[2]

Pneumoperitoneum has not been extensively studied as a therapeutic means of combating postsurgical overdistention, but it would appear to be a valuable adjunct to the treatment of this condition. Its chief disadvantages are that it requires long term maintenance and is poorly tolerated by some individuals. Pneumothorax also shares the disadvantage that it has to be continuously maintained.

Thoracoplasty appears to us to be the most attractive therapeutic device because it does not have to be maintained and because it does not involve the use of foreign bodies, e.g. air, oil, or plastic prosthesis—all of which carry potential hazards. The use of modified thoracoplasty in which the first rib and the transverse processes are left intact minimizes the amount of scoliosis which is in part, at least, responsible for decreased ventilatory function.

SUMMARY

1) Pulmonary overdistention is not always an irreversible process. Therapeutic response may be obtained even when overdistention has been established over relatively long periods of time.

2) The clinical improvement in patients who have overdistention has been documented by improvement in ventilatory function studies in four patients.

3) Clinical improvement in one patient which was not evident by improvement in ventilatory function studies suggests that occasionally there are other, immeasurable, factors to be dealt with.

4) The prevention of overdistention is to be preferred rather than treating overdistention once it has developed.

5) Modified space obliterating thoracoplasty appears to be the most effective and desirable procedure to prevent overdistention.

6) The efficacy of pneumoperitoneum has been demonstrated and, we believe, that it has a therapeutic place in our armamentarium.

RESUMEN

1) La sobredistensión pulmonar no es siempre un proceso irreversible. Puede obtenerse una respuesta terapéutica aún cuando la sobredistensión se ha establecido por periodos relativamente largos.

2) La mejoría clínica de los enfermos con sobredistensión, se ha hecho evidente por estudios de la función ventilatoria en cuatro enfermos.

3) La mejoría clínica en un enfermo en el que no pudo ponerse en evidencia mejoría de la función ventilatoria, sugiere que en algunos casos hay otros factores, no estimables, que intervienen.

4) La prevención de la sobredistensión, es de preferirse al tratamiento de ella una vez instalada.

5) La toracoplastía, obliterando el espacio, parece ser el medio más apropiado y deseable para evitar la sobredistensión.

6) Se ha demostrado la eficacia del neumoperitoneo y, creemos, que tiene un lugar terapéutico entre los recursos útiles.

RESUME

1) L'hyperexpansion pulmonaire n'est pas toujours un processus irréversible. On peut obtenir des succès thérapeutique même quand l'hyperexpansion existe depuis une période relativement longue.

2) L'amélioration clinique chez les malades atteints d'hyperexpansion pulmonaire à été confirmée par les progrès de la fonction respiratoire qui à pu être étudiée chez quatre malades.

3) L'existence de progrès cliniques chez un malade pour lequel la fonction ventilatoire n'avait pas semblé améliorée, fait entrevoir qu'il faut compter avec des facteurs impossibles à mesurer.

4) Il vaut mieux prévenir l'hyperexpansion que la traiter lorsqu'elle se développe.

5) La thoracoplastie semble être le procédé le plus efficace et le plus souhaitable pour éviter l'hyperexpansion. Grâce à elle, on obtient l'oblitération de la cavité dans laquelle le poumon à tendance à se développer anormalement.

6) On à démontré l'efficacité du pneumopéritoine, et les auteurs lui attribuent une certaine place dans l'armement thérapeutique.

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Pericardial Coelomic Cyst

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Although slightly more than 60 surgically proved cases have been reported in the English literature, pericardial coelomic cyst remains a relatively rare condition. In the interval since Pickhardt's description in 1934[1] of the first successful removal of such a tumor until the present, internists, surgeons, and radiologists have become more cognizant of this form of cystic disease within the chest. The reader's time will not be consumed by a lengthy review of the literature on the subject. He is referred to excellent papers by Cushing,[2] Lambert,[3] Bradford, Mahon and Grow,[4] Lillie, McDonald and Clagett,[5] Bates and Leaver,[6] Forsee and Blake,[7] and others. A case which recently came under our observation which was diagnosed pre-operatively, will be reported.

Case Report

N. R., a white female, age 28 years, employed as a medical secretary, complained of a moderately severe cold in her chest early in November 1951. This was accompanied by sharp, pleuritic pains in the lower right chest posteriorly and a severe non-productive cough. She had had a previous attack of pleurisy 12 to 13 years ago but could not remember on which side it has occurred. Other than this, there was no history of previous respiratory or cardiac illness. Her past history revealed an appendectomy in 1931, a tonsillectomy and adenoidectomy in 1932, and removal of an ovarian cyst with lysis of adhesions in 1947. Physical examination at the time of the current illness disclosed a few rales and a friction rub over the lower right chest posteriorly. There were no changes in breath sounds or physical signs over the anterior chest on either side. There was no fever.

Radiographic examination of the chest on November 14, 1951 in the postero-anterior and right lateral projections showed both diaphragms normal in contour. The heart was not enlarged. The left lung was clear. The right lung showed a sharply circumscribed shadow of homogeneous density, measuring about 4 x 5 x 7 cm., in the cardio-phrenic angle, lying in contact with the cardiac shadow and the anterior chest wall. The posterior border of the density was rounded and well-defined but the lateral border faded out gradually toward the periphery of the lung field. No fluid-levels or calcium densities were noted in the area involved.

The patient was sent home to bed and placed on terramycin. Re-examination on November 16, 1951 (Figure 1), showed no discernible change in the density of the lesion in the right cardio-phrenic angle but there was noted slight blunting of the costo-phrenic angle posteriorly with minimal hazy density in this area suggesting acute pleurisy. She returned to work one week after the first x-ray films were made, feeling much improved but still having some cough and slight chest pain posteriorly on the right side.

A previous single postero-anterior film of the chest (Figure 2), made sometime in the summer of 1948 was obtained. This film revealed a similar density in the same location as on the current film. It was less well-defined, however, and the chest was reported at that time as showing no abnormality. On December 24 1951 the chest was re-x-rayed, and the tumor mass appeared unchanged. The

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minimal pleural changes posteriorly had cleared. A radiographic diagnosis of pericardial coelomic cyst was made.

On January 8, 1952 the patient was admitted to the Buffalo General Hospital, and on January 10, 1952 right thoracotomy was performed. The operative report follows:

With the patient on the left side, a right antero-lateral incision was made along the sixth interspace and the thorax was opened. Digital exploration revealed a cystic structure lying in the lower anterior mediastinum. A segment of the fifth rib at the costo-chondral junction was removed and rib spreaders inserted. The cystic structure, measuring about 2 x 5 inches, could then be visualized. It was smooth, rounded and lay over the dome of the right diaphragm, being attached at the cardio-phrenic angle. With gentle traction on the cyst, it was apparent that it was arising from the pericardium to which it was attached by a broad base measuring approximately one and one-half inches in diameter. By means of careful, sharp dissection, and after the mediastinal pleura on the anterior surface of the cyst was incised, a line of cleavage was obtained. The cyst was then gently dissected from the pericardial attachment after severing the pleura around the entire circumference of the cyst. It was removed intact and was smooth, glistening and appeared translucent. There were a few bleeding points at the edge of the pericardium. These were clamped and tied with plain catgut ligature. Inspection showed adequate hemostasis, and the thorax was closed in the usual manner. A snug dressing was applied.

The pathological examination of the specimen (Figure 3), showed an ovoid, thin-walled, transparent cystic structure which measured 8 x 5 x 4 cm. There was one small amount of fat tissue attached to the surface in one area. Microscopic sections through the wall showed a serous cyst with a thin, fibrous wall lined by simple columnar and flattened epithelium.

The early post-operative course was uneventful except for the usual discomfort in the operative region. An x-ray film on January 14, 1952 showed the left diaphragm clear and regular. The right diaphragm was elevated and there was some

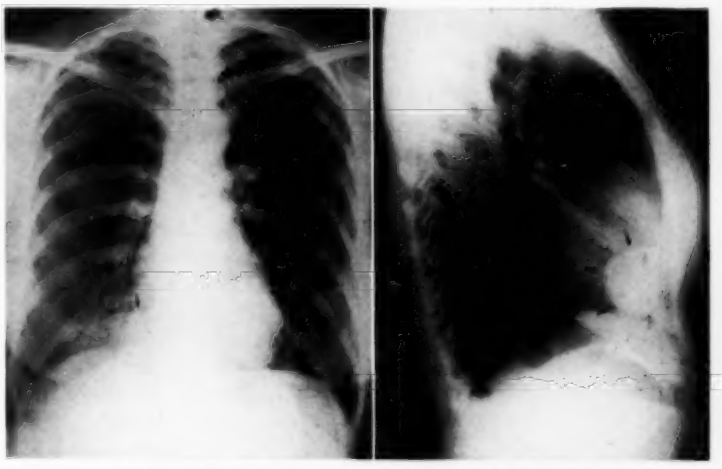

FIGURE 1A FIGURE 1B

Figure 1A: Postero-anterior film of the chest made November 16, 1951. The upper margin of the cyst is indicated by arrows.—*Figure 1B:* Right lateral film of the chest made November 16, 1951. The typical location of the cyst in the anterior mediastinum is clearly shown.

FIGURE 2 FIGURE 3 FIGURE 4

Figure 2: Chest film made in 1948. The margin of the cyst is poorly defined; the film was read as showing no abnormality.—*Figure 3:* Photograph of the surgical specimen removed from the right hemi-thorax January 10, 1952. Note its relative size.—*Figure 4:* Follow-up film of the chest made August 4, 1952.

pleural density overlying which probably represented a small amount of pleural fluid. The lung above was expanded and clear. The left chest was clear. On January 19, 1952 the pain in the right chest became severe and knife-like in character. An x-ray film on January 21, 1952 showed a slight increase in the amount of pleural density at the right base but there was no appreciable mediastinal shift. The left lung remained clear. The temperature curve was essentially normal except between January 22 and January 26, when it varied between normal and 101 degrees F. A blood count on January 24, 1952 showed 4,000,500 erythrocytes, 15.6 gms. of hemoglobin, and 10,000 leukocytes with a differential count of 12 bands, 76 filaments, 11 lymphocytes, and one monocyte. A chest film made on January 26, 1952 showed considerable increase in the amount of fluid in the right pleural space which filled in almost half of the hemi-thorax. There was no appreciable mediastinal shift. The left lung remained clear. On the same day 750 cc. of clear, amber fluid were removed from the right chest. This was cultured but showed no growth of organisms. After the thoracocentesis, she gradually became afebrile, breathing became less labored, and her chest pain diminished. She was discharged on February 2, 1952 feeling much improved but still having some residual pleural pain on the right side. A follow-up film of the chest made on August 4, 1952 showed slight elevation of the right diaphragm and minimal blunting of the costo-phrenic angle (Figure 4). Both lung fields were clear and the heart and mediastinum were not displaced.

Discussion

Pericardial coelomic cyst is more often than not a silent lesion. It is usually disclosed, as in this case, by radiographic examination of the chest as a routine measure or in search of evidence of other forms of disease or injury. Earlier writers stated that the condition produced no symptoms. However, as more and more cases were reported, it became apparent that many patients not only gave a history of one or more symptoms but that they also experienced partial to complete relief after surgical removal of the tumor. Lillie, et al.[5] reviewed 12 cases from the Mayo Clinic between 1941 and 1947, of whom six were asymptomatic. The remainder had such complaints as dyspnea, sub-sternal pain on exertion, "fluttering" of the heart, a tight feeling in the chest, tachycardia and precordial pressure, dull intra thoracic pain of long duration, and pressure over the heart after eating. Bradford, et al.[4] reported eight cases, of which three had varying symptoms of pain in the chest, dyspnea, productive cough, and vague pains in the left upper quadrant of the abdomen which occurred after eating and became more severe on lying down. In Forsee and Blake's series of 11 cases,[7] six had symptoms referable to mediastinal pressure or alteration in the normal pulmonary or cardiac physiology. Lam's case,[8] in which the tumor was unusually large, had a 10 year history of dyspnea, fatigue and angina pectoris, and was thought to have congenital heart disease. She made an excellent recovery after removal of the cyst with disappearance of symptoms. Reports of other authors describe symptom-complexes of a similar nature as those mentioned above.

Except in those cases with extremely large tumors, physical signs are notably lacking, even though the shadow on the roentgenogram is of sufficient size to be clearly visualized. Changes in percussion note are minimized because of the lesion's proximity to the heart, and are therefore

of little help in physical diagnosis. Auscultation is valueless, as any tumor or mass containing static fluid precludes the production of a bruit or adventitious sound.

It is, therefore, the chest roentgenogram which gives us the most valuable signs from which the condition may be suspected. Postero-anterior and lateral films usually suffice for good visualization of the lesion, but oblique and lateral decubitus projections may yield additional and helpful information. The exposures should be made at the point of maximum inspiration. Even a slight elevation of the diaphragm may minimize the density cast by the cyst, resulting in its being unobserved. This was the experience in our case, as the condition was not suspected from the film made in 1948.

Most characteristically, a pericardial coelomic cyst appears on the chest film as a round or ovoid shadow of homogeneous density, lacking in any calcific elements, which is situated in the anterior mediastinum at one of the cardio-phrenic angles. The mass is sharply defined on at least one projection even though it may appear to blend with the lung parenchyma in other views. It intimately approximates the anterior chest wall or diaphragm, or both, resembling a localized collection of encapsulated fluid. A most important feature is that it is always in contact with the cardiac silhouette. Lillie, et al.[5] state that two-thirds of the cases reported occurred at the cardio-phrenic angles, with the remainder lying at a higher level in the anterior mediastinum. Twice as many occur on the right side as on the left. Of the right-sided lesions, 75 per cent or more are situated at the angle. Of the left-sided lesions only about 40 per cent show a predilection for this same location.

Until the publication of Lambert's paper in 1940,[3] in which he presented two cases of Dr. Frank Berry and one of Dr. E. F. Butler, the pathogenesis of pericardial coelomic cysts was not well understood. His theory as to their origin is currently accepted as the most plausible, and, undoubtedly, is the correct one. A verbatim reiteration of what he has so precisely written is superfluous but his thought might be crystallized in a few words. When one of the primitive lacunae, which develops from the mesenchymn both lateral and ventral to the primordial ectodermal plate, fails to fuse with the remainder to form the pericardial coelom, it develops into an independent cavity or cystic structure attached to the pericardial coelom. Grossly, such a cyst appears as a smooth, thin-walled, glistening tumor mass, spherical in shape, and containing a watery, serous fluid which renders it almost transparent. The mass is covered with mediastinal pleura and is attached to the pericardium by a pedicle or base of varying size through which it receives its blood supply. At surgery, the cyst is seen to be entirely free of the adjacent portion of the lung and a distinct line of cleavage may be found between it and the pericardium, making enucleation an easy procedure. The significance of this fact will be mentioned in the discussion of a differential diagnosis. Microscopically, the cyst wall is composed of fibrous or collagenous tissue containing a few scattered

lymphocytes and vascular channels. The lining membrane consists of a single layer of cuboidal to flattened epithelial cells morphologically similar to the mesothelial cells lining the pericardium.

As many cystic tumors are located in the mediastinum a differential diagnosis is worthy of mention. To be considered are all the congenital lesions, namely, epidermoid, dermoid, teratoid, bronchial, esophageal, gastro-enteric cysts and cystic lymphangioma as well as the more common varieties of lipoma, echinococcus cyst and eventration of the diaphragm. Occasionally rare malignant lesions produce somewhat similar shadows on the roentgenogram. Bates and Leaver[6] reported two such cases, one of which proved to be a spindle-cell endothelioma and the other a probable papillary adenocarcinoma of undetermined origin.

The epidermoids are lined with stratified epithelium and their walls are made up of dense fibrous tissue, with or without glands of ectodermal origin. They are filled with a clear or milky fluid, or with a gelatinous material frequently mixed with hair. Dermoids are of a similar nature but in addition to the ectodermal structures exhibit tissues of mesodermal origin such as cartilage, bone, teeth, or smooth muscle. The teratomas are usually more solid in nature, and show histological elements of all three primary germ layers. Glandular elements of the alimentary and respiratory tract, as well as ectopic thyroid and thymic tissue may be found in addition to the contents of dermoids as mentioned above. Bronchial, esophageal and gastro-enteric cysts show a histological structure resembling that of the normal viscus. Cystic lymphangioma differs little microscopically from pericardial coelomic cyst except that on occasions cholesterol crystals are found in the fibrous wall. Grossly, there are singular differences. The lymphar iomas are multilocular tumors, intimately adherent to all surrounding structures, especially the pulmonary tissue. They receive their blood supply from adjacent tissues over their entire surface area. This fact makes complete exterpation almost impossible because the profusely bleeding vascular bed produces a serious surgical problem. Echinococcus cysts show a characteristic lining membrane which readily identifies them. They too, are often multilocular. Lipoma and eventration of the diaphragm often cannot be differentiated from a cystic structure.[9]

Of all the above mentioned lesions, only the dermoids and teratomas may, on occasion, show roentgen evidence of their contents. One can readily understand then, that a positive pre-operative is impossible. This can be achieved only by removal of the tumor and pathological examination of the specimen. With intra-tracheal anaesthesia, in which intra-pulmonary pressures may be accurately controlled and varied at will, giving the surgeon ample operating room, such cysts may be easily and safely removed. Even though all the evidence at hand is strongly presumptive of a pericardial cyst, and even though such a lesion is always benign, the low morbidity and mortality rate makes exploration imperative. The error of procrastination, should the suspected lesion be malignant, can never be rectified and may cost the patient his life.

SUMMARY

A case of pericardial coelomic cyst which was diagnosed pre-operatively is reported. The varied symptomotology, the paucity of physical signs and the importance of the roentgen findings are discussed. The pathogenesis of such cysts and their differential diagnosis is briefly reviewed. Inability to establish a positive diagnosis in all cases stresses the fact that surgical removal should be the only accepted form of treatment.

RESUMEN

Se relata un caso de quiste pericárdico celómico que fué diagnosticado antes de la operación. Se discuten la sintomatología variada, la escasez de signos físicos y la importancia de los hallazgos radiológicos. La incapacidad de hacer el diagnóstico en todos los casos recalca el hecho de que extirpación quirúrgica es la única forma de tratamiento.

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Post-Graduate Session—Compensation Court

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Concentrated lectures and panels in a postgraduate course produce returns that diminish in proportion to the length of the course. Introduction of student participation sessions can often refresh the interest of the group. A class compensation board, using compensation cases from the files of previous years, offers a method of developing this student participation. Pulmonary diseases lend themselves nicely to such a method of presentation.

While a great many compensation judgements rest on legal details, the basic principles of disease are of fundamental importance. In silicosis, for example, each state may have its own legal attitude toward the disease, but basic to that are certain medical pre-requisites. Such pertinent medical factors include, (1) length and type of dust exposure, (2) roentgenologic vs. clinical diagnosis of the disease, (3) symptomatic vs. asymptomatic silicosis, (4) progression of the disease, (5) prognosis, (6) relation to further irritants, (7) rehabilitation, (8) relationship to tuberculosis and other pulmonary diseases, and many others. The major testimony and conflicts in compensation cases are medical, with physicians the principle witnesses.

Other pulmonary diseases viz. spontaneous pneumothorax, malignancy, bronchiectasis, the fungus diseases, siderosis, berryliosis, Shaver's disease, bagasse disease and chest trauma are diseases appearing frequently before the compensation boards of the country. Like silicosis, they lend themselves to a class consideration of this sort.

The method we have employed is to use actual cases from the files of the State Compensation Board, and present the plaintiff's cause and his x-ray findings for the student court to consider. Many of the group are frequently willing to pass judgement without any further clinical data or investigation. Others, however, with greater knowledge of the disease, rise to the occasion and suggest further pertinent medical considerations—an effective way to emphasize the significance of such information. This in turn, can be developed into a rather active discussion of the disease involved. Concern for the rights of the patient serves as the human-interest catylist to the discussion.

The crux of each case has been in having the compensation commissioner himself present to give and explain the final decision of the State Board and the reasons for that decision. This too, while it may involve some legal technicalities, frequently adds further pertinent medical considerations of the disease in question.

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*Assistant Professor of Medicine, University of Buffalo School of Medicine and Department of Medicine, Buffalo General Hospital.

The tenth in a series of articles prepared under the sponsorship of the Council on Undergraduate Medical Education of the American College of Chest Physicians.

This approach has several advantages, the first of which is class participation which can be refreshing and quite enjoyable. The group, with moderate assistance, serves to teach itself, just as group therapy is effective with patients. It also promotes the airing of misimpressions, and correction of such misinformation is as important as acquiring new material (a side of postgraduate teaching that is usually overlooked).

This approach also serves well to introduce an interest in pulmonary diseases to physicians not primarily concerned with that specialty. Medical specialization has developed an unfortunate segregation of medical thought which is reflected and overemphasized in medical meetings and courses. We spend a good deal of time talking to ourselves and to men with similar experiences and interest. This compensation court method offers one means of cutting across specialty lines. Our own presentation has been for an occupational hygiene course intended for industrial physicians, many of whom do not attend chest sessions as a rule.

Editorial

CYTOLOGIC DIAGNOSIS OF LUNG CANCER

SEYMOUR M. FARBER, M.D., F.C.C.P.
San Francisco, California

The application of cytologic techniques to the diagnosis of cancer of the lung is about seven years old; the accumulation of substantial clinical studies since 1947 have demonstrated that cytology deserves to be considered one of our primary diagnostic techniques for this disease. Nevertheless, there are an insufficient number of laboratories utilizing this technique.

This neglect is unfortunate and, further, difficult to understand. At the present time, cytology promises morphologic diagnosis of perhaps twice the percentage of lung cancers that are now so diagnosed by bronchoscopy; further, a greater percentage of cancers diagnosed by cytology are amenable to surgery than those diagnosed by bronchoscopy. The method is very easily applied by the physician, and it is relatively inexpensive. The equipment it requires is already on hand in every laboratory. It requires two things: (1) That a laboratory technician undertake three or four months training in a laboratory where the method is already practiced, and, (2) That a pathologist become thoroughly acquainted with cytologic appearances, which differ from those seen on tissue sections.

One suspects that the reluctance to establish facilities for cytologic diagnosis of lung cancer is a part of the lethargy which one frequently meets when the subject of lung cancer is introduced. It is true that the mortality rate for this disease remains discouragingly high, however it is approached. On the other hand, one cannot diagnose and treat individual patients in terms of statistics. Five-year survivals have been secured by means of surgery; every patient in whom lung cancer is suspected must be regarded, then, as a potential five-year cure. The medical profession cannot neglect promising diagnostic techniques because the overall recovery rate is low. Statistics are valuable but they cannot be allowed to determine the attitude toward the individual patient.

There is no reason to think that the present application of cytology exhausts its possible service in the diagnosis of lung cancer. In recent series a diagnostic accuracy of 90 per cent has been secured among large series of lung cancer cases. It has been further observed, however, that the efficiency of this method is probably greater among early cases, in which the bronchial passages are not yet occluded, than in late ones. This suggests that the greatest application of cytology may yet prove to be as a routine screen device. Its convenience for the patient and physician and its inexpensiveness make its routine use in anual or semi-annual checkups entirely feasible. Surgical cure rates might be expected to show a major improvement if cytology were so used. Only the lack of facilities and interested personnel prevent us from investigating this possibility.

RICHARD H. OVERHOLT

Presentation of the College Medal for 1954 to Dr. Richard Hollis Overholt*

BURGESS L. GORDON, M.D., F.C.C.P.**
Philadelphia, Pennsylvania

Mr. President, Members of the College, Ladies and Gentlemen:

I am pleased, Dr. Greer, to have the privilege of speaking for the American College of Chest Physicians in the presentation of the College Award to Dr. Richard Hollis Overholt. Among the eight distinguished recipients of this, the highest honor conferred by the College, Dr. Overholt belongs to a small group, hardly more than a dozen, who early in their medical transcendency made thoracic surgery the major field of endeavor. In adding another illustrious physician to the College hall of fame, the Committee on Award has very appropriately expressed the appraisal, not only of the College, but of other important segments of American medicine.

As I look upon you, Dick, standing here, about to receive this College Medal, I realize that fancy plays an embarrassing trick by carrying me back over quite a few years to the occasion when I first met you. On this particular morning, you were speaking about the potentials of pulmonary resection. Indeed there was skepticism, for there remained the hazards of atelectasis, spreading infection, and faulty anesthesia. It is a matter of great interest that the events proved your concepts to be correct. You have removed with fine precision localized processes of bronchiectasis, tuberculosis, cystic disease, and even cancer of the lung. Your knowledge of anatomy and physiology—your imagination, ingenuity, refined techniques, and careful reporting have won for you the recognition of thoracic medicine and the gratitude of countless patients.

In this College are your friends and associates—some have watched from their vantage point of long experience and the knowledge of pioneer days; many have grown up with you; and not a few have been your pupils and assistants. You have earned our esteem, our confidence and respect.

Dick, I am very happy to hand you the College Medal. Along with it go the admiration and the affection of your fellow members of the American College of Chest Physicians.

BIOGRAPHICAL DATA

University of Nebraska School of Medicine, M.D., 1926.
Intern: University of Pennsylvania Hospital, Philadelphia, 1926-28.
Fellow in Surgery, University of Pennsylvania Hospital, 1928-31.
Staff, Lahey Clinic, Boston, Massachusetts, 1931-38.
Overholt Thoracic Clinic, 1101 Beacon Street, Brookline, Massachusetts, 1938.
Clinical Professor of Surgery, Tufts College Medical School, Boston, Massachusetts.
Thoracic Surgeon: New England Deaconess Hospital, Boston, Massachusetts.
Consultant: Norfolk County Hospital, Plymouth County Hospital, Cambridge Tuberculosis Sanatorium, Sassaquin Sanatorium, Rhode Island State Sanatorium, Barnstable County Hospital, Essex County Sanatorium, Bristol County Sanatorium, and New England Center Hospital.
President, American College of Chest Physicians, 1948-49.

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*Presented at Presidents' Banquet, 20th Annual Meeting, American College of Chest Physicians, San Francisco, June 19, 1954.
**Chairman, Committee on Awards.

College Chapter News

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4000 West Kentucky Ave., Tampa 7, Florida

L. C. Manni, M.D., Medical Director
W. T. Edwards Hospital
2323 Phillips Road, Tallahassee, Florida.

William L. Potts, M.D., Medical Director
Southeast Florida Tuberculosis Hospital
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Henry C. Sweany, M.D., Chief Medical Director
State Tuberculosis Board
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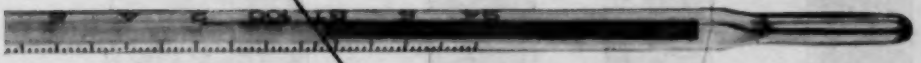

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1. Flippin, H. F.: Philadelphia Med. 49:733 (Jan. 30) 1954.
2. Glatt, M., and Ross, S.: Antibiotics & Chemotherapy 4:395 (Apr.) 1954.

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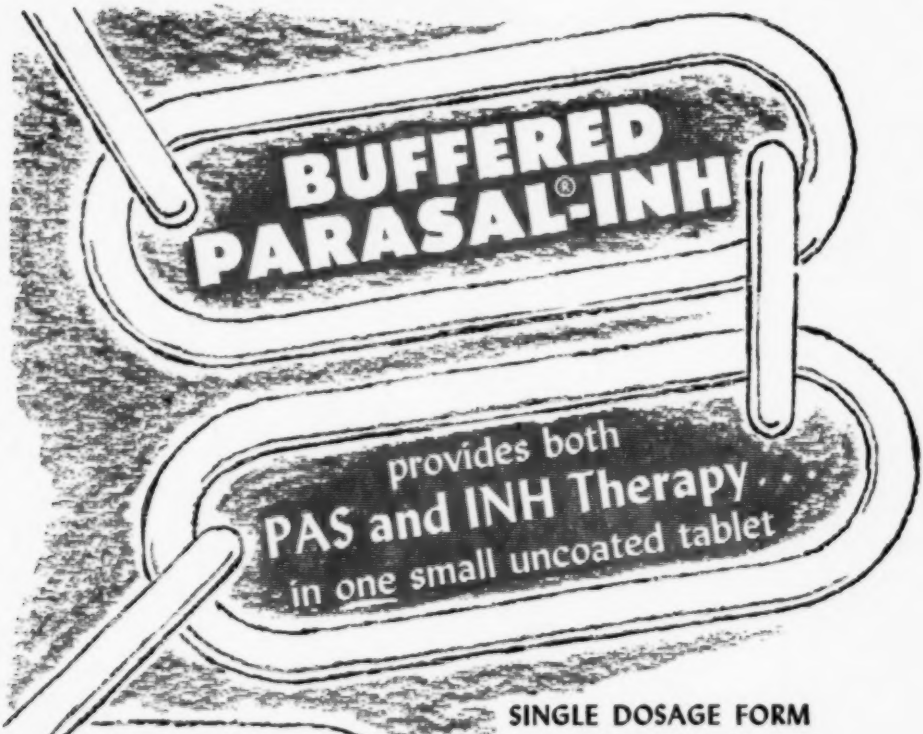

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